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A Systematic Review of the Cutaneous Adverse Effects of GLP-1 Agonists

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Abstract

Glucagon-like peptide-1 (GLP-1) receptor agonists, such as liraglutide, exenatide, and semaglutide, have gained widespread FDA approval in the past decade for managing diabetes and obesity. With nearly 22% of Americans inquiring about these medications and 15% reporting usage, GLP-1 agonists have demonstrated significant efficacy in normalizing blood glucose, improving cardiovascular profiles, and promoting weight loss. However, as the use of this drug class has expanded, reports of adverse effects, including panniculitis, bullous pemphigoid, and hypersensitivity reactions, have emerged in scientific literature. Despite these concerns, there is limited research addressing the demographics of patients experiencing these cutaneous adverse effects. This retrospective study aims to not only summarize the mechanisms and incidence of GLP-1-associated skin manifestations but also identify patient populations most at risk, providing insights to guide clinical decision-making and improve patient safety.

1. INTRODUCTION

Glucagon-like peptide-1 (GLP-1) receptor agonists are a class of medications that mimic the actions of the endogenous hormone GLP-1, resulting in enhanced glucose-dependent insulin secretion, decreased glucagon release, and delayed gastric emptying. Drugs in this class, including liraglutide, exenatide, and semaglutide, have revolutionized the management of diabetes and obesity by improving glycemic control and encouraging weight loss[1]. GLP-1 agonists initially received FDA approval for the treatment of type 2 diabetes mellitus two decades ago. More recently, drugs within this class became the first approved medications for chronic weight management, broadening their use within the general population. Recent polls indicate that approximately one in eight US adults (12%) have taken a GLP-1 agonist, with 6% reporting current use of these medications. The effectiveness of these medications in regulating blood glucose levels and promoting weight loss in individuals with and without diabetes has contributed to their rapid rise in popularity.

Despite demonstrating improved glycemic control and weight management, GLP-1 receptor agonists are associated with a range of adverse effects. The most frequently reported side effects are gastrointestinal symptoms, including nausea, vomiting, and diarrhea. These side effects are generally transient and improve with behavioral modifications, such as smaller portion sizes. Among GLP-1 agonists, liraglutide and exenatide are associated with the highest frequency of gastrointestinal complaints, including cases of acute pancreatitis[2]. This may be attributed to an increased release of pancreatic enzymes, a sequelae shown to cause delayed-onset acute pancreatitis in animal models. Additionally, immune-mediated responses,

including injection site reactions and anaphylactic events, though less common, are also notable and vary in prevalence across different GLP-1 receptor agonists[1]. These potential side effects are important clinical considerations for providers prescribing GLP-1 agonists, and patient qualifiers should be taken into consideration to determine which individuals are more at risk for developing specific adverse reactions.

Beyond gastrointestinal side effects, emerging literature highlights a variety of dermatologic manifestations associated with GLP-1 agonists; however, the mechanisms underlying these dermatologic reactions remain incompletely understood. The GLP-1 receptor, while predominantly expressed in pancreatic tissue, is present in various tissues throughout the body. Emerging evidence suggests GLP-1 receptors are upregulated in the skin under certain inflammatory conditions, where its expression is likely due to infiltration by immune cells that carry the receptor[3]. In certain individuals, GLP-1 agonists may cause an immunologic reaction to drug-protein complexes through autoantibody formation or T-cell reactivity, leading to dermal hypersensitivity or morbilliform drug reactions[4,5]. GLP-1 agonists are also implicated in drug-induced and drug-triggered forms of bullous pemphigoid (BP) likely through a similar method of autoantibody formation against hemidesmosomes[6,1,7]. Furthermore, the role of GLP-1 agonists as an epigenetic modifier of cellular pathway signaling may contribute to other cutaneous manifestations, including alopecia and facial aging[8,9]. Multiple of these dermatologic adverse reactions are reported in the literature, raising concerns about the broader impacts these drugs have on skin health. In some cases, however, GLP-1 agonists may exhibit a protective effect against cutaneous pathology, such as neoplasms[10]. Despite these concerns, the overall dermatologic safety profile of GLP-1 agonists remains under investigation, with both negative and potentially beneficial outcomes emerging in the literature. This review aims to summarize and analyze the existing studies on the cutaneous manifestations of GLP-1 receptor agonists, exploring both common presentations and underlying mechanisms. By synthesizing the current literature and identifying important patient qualifiers, this review will serve as a foundation for future research with the goal of improving dermatologic outcomes in patients using GLP-1 agonists.

2. DISCUSSION

2.1. Alopecia

The pathophysiology of alopecia is multifactorial and involves an environmental insult on a genetically susceptible individual, leading to a disruption in the growth cycle of hair follicles. Rapid weight loss, as seen in individuals using GLP-1 agonists, may cause significant stress on the body through decreased availability of glucose, which is capable of sending hair follicles prematurely into their resting phase known as telogen [11]. The resultant shedding of hair, known as telogen effluvium, can occur approximately 2-3 months after the inciting event. Alternatively, GLP-1 agonists can trigger androgenic alopecia through the disruption of hormonal pathways, particularly through modulation of insulin-like growth factor-1 (IGF-1). Dermal papillae cells within the scalp secrete IGF-1, which is essential in promoting hair growth as well as hair shaft differentiation. The absence of IGF-1 induces catabolism of the hair follicle[12]. Though the exact mechanism is unknown, Panchaprateep et al. suggests that GLP-1 agonists downregulate the production of IGF-1 in dermal papillae, leading to a shortened hair growth, or anagen, phase[13]. Patients with alopecia following GLP-1 agonist use may experience significant hair shedding and thinning; however, these medications may actually promote hair growth in certain populations. Steady declines in weight loss lead to increased testosterone. Though elevations in testosterone are often associated with hair loss, the increases in testosterone secondary to steady weight loss reach a hormonal balance as insulin levels decline. Enabling insulin sensitivity leads to an enhancement in vasculature and blood flow to the skin, improving hair growth[12]. Through this mechanism, individuals with type 2 diabetes mellitus undergoing treatment with GLP-1 agonists may experience hair growth benefits.

Although GLP-1 agonists modulate hair growth through various mechanisms, there is clinical evidence to support that alopecia may be a side effect of treatment. A scoping review of 22 articles, including 15 clinical trials, 6 case reports, and 1 retrospective cohort study was evaluated to investigate the dermatologic effects of GLP-1 agonists[14]. Alopecia was reported in 6.9% of patients on oral semaglutide, as compared to 0.3% of patients being treated with a placebo. Meanwhile, only 0.2% of patients on subcutaneous semaglutide developed alopecia, as

compared to the 0.5% in the placebo group. The difference in alopecia rates between oral and subcutaneous semaglutide may be either a dose-dependent effect or specific to the route of administration. Doses cannot be compared exclusively since oral semaglutide undergoes first-pass metabolism, which significantly impacts its bioavailability. Further research is necessary to better understand the relationship between alopecia and GLP-1 agonists, as well as the influence of dosing, route of administration, and patient qualifiers.

Given the potential link between GLP-1 agonists and alopecia, clinical consideration of medication prescription requires reviewing benefit-harm modeling studies to determine if treatment is advantageous for different patient populations. Moll et al. conducted a literature search and meta-analysis to determine benefit versus harm outcomes in those being treated with GLP-1 agonists[15]. Inclusion criteria consisted of patients 18 years of age or older, without diabetes, and a BMI of greater than 27 kg/m^2 with weight-related comorbidity. Harm outcomes in individuals undergoing GLP-1 agonist therapy included alopecia, with a relative risk of 5.67. Specifically, alopecia was associated with an increased risk in those being treated with tirzepatide as compared to those treated with semaglutide and liraglutide[15]. Tirzepatide has dual agonism of both GLP-1 and glucose-dependent insulinotropic polypeptide (GIP) receptors, leading to enhanced downregulation of insulin and IGF-1 hormones. Through modulating the androgenic pathway of alopecia, this mechanism likely contributes to the increased rate of alopecia seen in the tirzepatide treatment group.

While Moll et al. provides evidence that supports the GLP-1 induced androgenic mechanism of alopecia, it excludes individuals being treated for diabetes. Comparing the rates of alopecia in patients treated with GLP-1 agonists to other anti-diabetic medications can help determine whether certain patient populations, such as those with type 2 diabetes, experience a protective effect on hair growth. When compared to other diabetic therapies, most GLP-1 receptor agonists appear to exhibit a protective effect against alopecia, which is similar in comparison to treatment with sodium-glucose cotransporter-2 inhibitors (SGLT2i)[16]. The odds ratio for alopecia with GLP-1 agonists overall is 0.61, suggesting a 39% lower likelihood of developing alopecia. The odds ratio for alopecia with SGLT2i is 0.41, indicating a 59% decreased likelihood. Though SGLT2i are associated with less risk of developing alopecia, this difference is not statistically significant. Interestingly, semaglutide has an odds ratio of 1.24, indicating those using semaglutide therapy are 1.24 times more likely to develop alopecia. To summarize, both GLP-1 agonists and SGLT2i generally lower the risk of alopecia, but semaglutide is an exception, posing an increased risk. The data indicates a potential protective relationship between antidiabetic medications and alopecia in individuals with type 2 diabetes[16]. However, specific medications within this class may have active metabolites that act peripherally to facilitate alopecia. More research is necessary to better understand how patient qualifiers, like type 2 diabetes, affect dermatologic manifestations of GLP-1 agonists. Additionally, there is a lack of information in the literature to indicate a time-to-onset, location, and recovery of alopecia after discontinuing the offending GLP-1 medication. These gaps in knowledge require further investigation to improve provider knowledge and patient education when prescribing GLP-1 agonists. Adverse effects, especially those of cosmetic consequence, will likely deter patients from being compliant in their treatment which may be detrimental to their health.

2.2. Cutaneous Neoplasms

Emerging literature suggests there may be a relationship between GLP-1 agonists and carcinogenesis. GLP-1 agonists potentially contribute to the formation of cutaneous neoplasms through the upregulation of mitogenic signaling pathways in melanocytes and keratinocytes[17]. GLP-1 agonists, such as geniposide, are shown to upregulate receptor tyrosine kinases, particularly c-kit, in a dose-dependent manner. C-kit enhances melanogenesis, thereby promoting an environment suitable for melanocytic proliferation through constitutive activation of mitogenic signaling pathways[18]. Additionally, GLP-1 receptors are present in adipocytes, and the activation of these receptors through GLP-1 agonists can cause stem cell differentiation[19]. Alteration of these stem cells can lead to carcinogenic traits in keratinocytes as well as fibroblasts, suggesting a potential role for GLP-1 agonists in tumor pathogenesis.

Diabetes and obesity, however, are well-established risk factors for carcinogenesis, contributing to a pro-tumorigenic environment through hyperglycemia, hyperinsulinemia, chronic inflammation, and increased oxidative

stress[20]. Effective management of these chronic conditions, particularly by maintaining glucose homeostasis, can indirectly inhibit cancer proliferation. GLP-1 agonists may prevent carcinogenesis through improved glucose metabolism and decreased IGF-1 signaling, which reduces mitogen-activated protein kinase activity[20]. Additionally, GLP-1 agonists inhibit epidermal-like growth factor, a pro-growth signaling pathway leading to uncontrolled cell division[10]. Through both indirect and direct mechanisms, GLP-1 agonists may confer a protective effect against carcinogenesis; however, their ability to upregulate c-kit signaling and promote adipocyte stem cell differentiation suggests a potential pathologic role in the development of melanoma and non-melanoma skin cancers. Given that GLP-1 agonists influence numerous cellular pathways, the relationship between GLP-1 agonists and cutaneous neoplasms remains incompletely understood.

Controlled trials, observational studies, and meta-analyses have not consistently found a clear association between GLP-1 agonists and skin cancer. The LEADER trial investigated the effect of liraglutide compared to placebo on the development of neoplasms in individuals ≥50 years old with type 2 diabetes and high cardiovascular risk. Non-melanoma skin cancer emerged as the most frequently occurring neoplasm across both arms of the study, affecting 1.5% of individuals compared to a prevalence of 0.787% in the general US population[21]. The rate of non-melanoma skin cancers in the study population may be expected given the average age of the study participants and the risk of carcinogenesis associated with type 2 diabetes. After one year of randomized treatment, those being treated with liraglutide experienced malignant melanoma at a 10.95 times higher rate than the placebo group. After two years of treatment, the difference between groups narrowed with a 4.97 times higher rate in the liraglutide group, a statistically insignificant difference[21]. This study was limited by short follow-up times (median = 3.8 years) and specific patient criteria that make understanding long-term side effects of GLP-1 agonists and generalizing these findings difficult.

Compared to other anti-diabetic medications, GLP-1 agonists are not associated with an increased risk of cutaneous neoplasms. Pradhan et al. compared the prevalence of melanoma and non-melanoma in individuals being treated with either GLP-1 agonists or sulfonylureas, an anti-diabetic medication that stimulates pancreatic insulin secretion. Patients included were ≥18 years old receiving monotherapy for type 2 diabetes. Data from 11,786 patients on GLP-1 agonists and 208,519 patients on sulfonylurea monotherapy were included. Statistical analysis revealed no association between melanoma or nonmelanoma skin cancers with GLP-1 receptor agonists or sulfonylureas for diabetes management[22]. While the magnitude of this study allows for generalizability to the UK patient population, the absence of a placebo group limits the ability to definitively exclude an association between anti-diabetic therapies and cutaneous neoplasms, whether resulting in improved or worsened outcomes.

Recent literature suggests that GLP-1 agonists may protect against non-melanoma skin cancer, specifically basal cell carcinoma. Sun et al. developed a Mendelian randomization study to assess for a causal relationship between GLP-1 receptor activation and carcinogenesis. Through meta-analysis combining the data from Mendelian randomization and an extensive European genetic database, researchers determined that higher expression of GLP-1 receptor genes is associated with a protective effect against basal cell carcinoma[23], indicating the use of GLP-1 agonist drugs may also decrease the incidence of these non-melanoma skin cancers. When correlating these results to randomized controlled trials, GLP-1 agonists do not reduce the incidence of basal cell carcinoma after 3.2 years of follow-up, on average[23]. As previously stated, the long-term sequelae of GLP-1 agonist use are poorly understood secondary to limited safety data surrounding neoplasms. The potential for long-term use as maintenance therapy in type 2 diabetics and individuals with obesity necessitates further research to establish a relationship between GLP-1 agonists and cutaneous neoplasms.

2.3. Hypersensitivity Reactions

Hypersensitivity reactions to GLP-1 receptor agonists are a significant, though relatively rare, subset of their adverse effects, with presentations ranging from localized dermal reactions to systemic anaphylaxis. These reactions warrant attention due to their potential to disrupt treatment regimens for type 2 diabetes and obesity, as well as their implications for patient safety. Dermal sensitivity in allergic cutaneous manifestations refers to the heightened skin response to allergens, leading to symptoms such

as redness, itching, swelling, hives, or eczema due to an overactive immune reaction[24]. Among the reported side effects, dermal hypersensitivity reactions have emerged as a notable concern, with 17 documented cases to date including 10 patients, warranting further exploration into their clinical significance and underlying mechanisms[4,5,17,25-34] . These cases highlight the complex interplay between immune responses and therapeutic proteins, emphasizing the need for rigorous evaluation and management strategies.

Localized hypersensitivity reactions are the most common cutaneous manifestations associated with GLP-1 receptor agonists. These reactions typically present as pruritic, erythematous plaques or maculopapular rashes at injection sites, often resulting from delayed-type hypersensitivity. For instance, a 35-year-old female using liraglutide for weight reduction developed mildly itchy erythematous plaques surrounded by ecchymotic patches at the injection sites within two weeks of therapy initiation[25]. While laboratory findings were within normal limits, the lesions resolved after discontinuing liraglutide, leaving firm nodules at the injection sites. Similarly, a 39-year-old male experienced delayed hypersensitivity with pruritic plaques after titrating liraglutide to the therapeutic dose of 3 mg daily[26]. Intradermal testing at a 1:10 dilution confirmed the hypersensitivity reaction, although patch testing yielded negative results. This delayed immune response is likely mediated by T-cells recognizing protein antigens in the therapeutic formulation, initiating cytokine-driven inflammation. Despite the reaction, the patient successfully continued liraglutide therapy with symptomatic management using topical corticosteroids, illustrating the feasibility of therapy continuation in select cases.

Systemic hypersensitivity reactions, while less common, represent a significant clinical challenge due to their severity. These reactions often involve IgE-mediated mechanisms or other pathways, such as complement activation. A 52-year-old male treated with exenatide exhibited urticaria, respiratory distress, and itching after repeated injections[27]. Intradermal testing confirmed exenatide hypersensitivity, while liraglutide testing was negative, suggesting variability in immunogenic responses between GLP-1 receptor agonists. Another case described a 34-year-old female who experienced urticaria and dysphagia within minutes of exenatide administration postpartum[28]. Skin prick tests confirmed an IgE-mediated mechanism, likely driven by mast cell degranulation and histamine release. The rapid onset of symptoms required immediate discontinuation of therapy and precluded further reintroduction, reflecting the importance of rapid recognition and management of systemic reactions.

Prolonged exposure to GLP-1 receptor agonists may also trigger delayed or cumulative hypersensitivity reactions, as evidenced by several cases. A 45-year-old female treated with dulaglutide developed delayed urticaria-like plaques confirmed through intradermal testing, pointing to a T-cell-mediated hypersensitivity pathway[29]. Another case involved an 84-year-old male who presented with a morbilliform eruption after two weeks of dulaglutide therapy[17]. Histopathology revealed interface dermatitis with eosinophilic infiltrates, supporting a delayed-type hypersensitivity diagnosis. These cases suggest that cumulative exposure to antigenic components in GLP-1 receptor agonists can exacerbate immune responses over time, potentially complicating long-term therapy.

The variability in hypersensitivity reactions among different GLP-1 receptor agonists underscores the importance of understanding cross-reactivity. A 61-year-old male experienced anaphylaxis to lixisenatide, including urticaria, dyspnea, and hypotension, despite previous tolerance to liraglutide[30]. Intradermal testing confirmed hypersensitivity to lixisenatide and exenatide, while liraglutide was well tolerated. Differences in molecular structure, such as the exendin-4 origin of lixisenatide versus the human GLP-1 analog structure of liraglutide, likely account for these variations. Another case series demonstrated that while most patients reacting to liraglutide tolerated semaglutide, one patient experienced severe anaphylaxis to semaglutide after transitioning from subcutaneous to oral administration[31]. These findings emphasize the importance of individualized allergological evaluations, including intradermal testing and basophil activation assays, to guide therapy selection.

Desensitization protocols have emerged as a viable option for patients with hypersensitivity who lack alternative treatment options. In one report, a seven-step desensitization protocol enabled two patients with immediate hypersensitivity to exenatide to tolerate therapeutic doses without complications[32]. The protocol gradually introduced increasing doses of exenatide over three hours, likely reducing mast

cell activation thresholds through immune regulatory mechanisms. While resource-intensive, desensitization provides a pathway for continuing essential therapy when hypersensitivity reactions threaten its discontinuation.

2.4. Panniculitis

Eosinophilic panniculitis is a rare inflammatory condition of the subcutaneous fat characterized by eosinophilic infiltration, fat necrosis, and variable fibrosis. It clinically manifests as tender, erythematous, or violaceous nodules or plaques, often accompanied by systemic symptoms such as fever or malaise, particularly when linked to systemic diseases or drug hypersensitivity[33]. Among the adverse effects of GLP-1 receptor agonists, 10 cases of panniculitis have been reported, each providing critical insights into its pathophysiology and clinical presentation[34–43]

Panniculitis associated with GLP-1 receptor agonists is frequently linked to the immune response elicited by poly(lactide-co-glycolide) (PLGA) microspheres used in sustained-release formulations. These biodegradable polymers hydrolyze over time, releasing the active drug while potentially triggering a foreign body reaction in susceptible individuals. For instance, a 38-year-old woman on sustained-release exenatide developed firm, erythematous nodules three weeks after initiating therapy[37]. Histopathological examination revealed eosinophil-rich granulomatous panniculitis with foreign material consistent with PLGA microspheres, confirmed via acid-fast staining. These findings demonstrate the role of PLGA microspheres in recruiting eosinophils and macrophages, leading to granulomatous inflammation. Such polymer-based reactions are rare but clinically significant, necessitating advanced diagnostic techniques like infrared spectroscopy and acid-fast staining for confirmation.

The clinical spectrum of panniculitis varies, with some cases presenting as localized nodules at injection sites and others involving more systemic symptoms. A 54-year-old male with a 17-year history of type 2 diabetes developed a tender subcutaneous nodule at an exenatide injection site after five months of therapy[38]. Biopsy findings revealed mixed lobular and septal panniculitis with multinucleated giant cells, lymphohistiocytic infiltrates, and abundant eosinophils, consistent with EP. Similarly, a 63-year-old female developed migratory subcutaneous nodules corresponding to exenatide injection sites[39]. Histological analysis demonstrated small amorphous materials surrounded by inflammatory infiltrates, later identified as PLGA microspheres via spectroscopy.

While panniculitis is often localized, systemic presentations have also been reported. A 42-year-old female developed myalgia, limb edema, and skin induration two weeks after initiating semaglutide for weight loss[40]. MRI findings indicated diffuse fascial inflammation consistent with eosinophilic fasciitis. Although no biopsy was performed, laboratory tests revealed peripheral eosinophilia, and the symptoms resolved following drug discontinuation and immunosuppressive therapy. This represents the first reported case of semaglutide-associated eosinophilic fasciitis and highlights the potential for systemic eosinophilic disorders linked to GLP-1 receptor agonists. Such cases emphasize the need for clinicians to remain vigilant for atypical manifestations, even when systemic symptoms initially seem unrelated to the drug.

Management of GLP-1 receptor agonist-induced panniculitis typically involves discontinuation of the offending agent and symptomatic treatment. For persistent or severe cases, interventions such as corticosteroids or intralesional injections may be required. A 60-year-old male with six persistent nodules on his abdomen and thigh following exenatide therapy achieved significant improvement with intralesional triamcinolone[41]. The treatment resulted in over 50% reduction in nodule size after six weeks, with near-complete resolution at follow-up. Similarly, a 63-year-old female with recurrent nodules after sustained-release exenatide was counseled on the nature of her reaction and managed with serial triamcinolone injections[42]. These cases highlight the efficacy of targeted therapies for localized panniculitis and the importance of individualized care in managing drug-induced adverse effects.

2.5. Bullous Pemphigoid

Bullous pemphigoid (BP) is the most common autoimmune subepidermal blistering disorder, initiated by autoantibodies targeting two hemidesmosomal proteins: BP180 and BP230. The disease's development is influenced by a combination of predisposing factors, including human leukocyte antigen (HLA) genes, existing comorbidities, aging, and specific environmental triggers. BP has often been linked to the use of systemic therapies. Frequently implicated medications include antibiotics, beta-blockers, non-steroidal anti-inflammatory drugs

(NSAIDs), diuretics, and more recently, anti-tumor necrosis factor (TNF)-α drugs and dipeptidyl peptidase 4 inhibitors (DPP-4i)[6]. Several case reports show GLP-1 agonist-induced BP and drug-triggered BP, indicating latency period from two weeks up to six months after anti-diabetic drug administration with resolution occurring shortly after drug administration cessation.

Five case reports appear in the literature detailing BP as an adverse effect of a GLP-1 agonist drug. According to Fukuda et al.,, a case of drug-induced BP was reported in a Japanese 62-year-old male eight weeks after administration of dulaglutide, insulin degludec, and metformin[44]. He developed pruritic erythematous lesions and biopsy confirmed subepidermal blisters. Elevated levels of anti-BP230 and anti-BP180 were present. Once BP was reported, dulaglutide was discontinued and prednisolone and minocycline were administered with no recurrence of lesions[44]. Similarly, according to Sonego et al., a case of drug-induced BP was reported in an 84-year-old female eight weeks after weekly dulaglutide subcutaneous administration for type 2 diabetes mellitus management[45]. She developed numerous tense bullous lesions with serous-hematic content over the entire skin area. Both antibody titers BP180 and BP230 were elevated. Notably, elevated levels of anti-BP180 and anti-BP230 were present in the patients with drug-induced and drug-triggered BP, respectively, but those levels were also elevated in patients without BP as well. However, these elevated levels may cause these patients to be more susceptible to drug-induced or drug-triggered BP[1]. BP resolved after discontinuation of dulaglutide and administration of prednisone and doxycycline[45]. Both cases suggest a latency period of eight weeks before the presentation of drug-induced BP and resolution of lesions with drug discontinuation and a combination of corticosteroids and antibiotic administration.

According to Schwager et al., a case of drug-induced BP was reported in a 64-year-old male six weeks after treatment with dulaglutide. He presented with urticarial lesions, tense bullae, pruritus, and erosions over bilateral upper and lower extremities. Dulaglutide was discontinued and the skin lesions resolved gradually after being treated with potent topical corticosteroids, resolving fully after three months[46]. According to Burruss et al., a case of drug-induced BP was reported in a 61-year-old female four weeks after beginning treatment with semaglutide in November 2020 for type 2 diabetes mellitus[47]. She presented with a single erythematous crusted lesion on her breast in December 2020 and then with new crusted erosions over the breast and lower back, combined with erythema and edema of the gingiva in January 2021. Skin biopsies of the lower back and breast showed subepidermal vesiculation with brisk mixed dermal infiltrate containing eosinophils. BP showed improvement shortly after discontinuing semaglutide without any additional treatments[47,14]). Lastly, Collins et al. reported a case of drug-triggered BP in a 75-year-old male 2 weeks after beginning liraglutide treatment for the patient's type 2 diabetes mellitus. He presented with a vesicular eruption on the head, neck, arms, and trunk lasting six months. The patient discontinued liraglutide and began doxycycline, showing improvement in the skin condition seven months after discontinuation of liraglutide[1].These five case reports of drug-induced or triggered BP demonstrate the onset of BP as early as two weeks and as late as six months after drug administration in subcutaneous formulations of GLP-1 agonists.

2.6. Facial Skin Aging

As GLP-1 agonists, such as semaglutide, have gained popularity for the treatment of type 2 diabetes mellitus and weight management, “semaglutide face” has become a popular term used to describe the noticeable facial volume loss and pre-aged features of patients on GLP-1 agonist[28]. Semaglutide received original FDA approval for glycemic control in type 2 diabetes; however, its ability to aid in rapid weight loss resulted in an additional FDA indication for chronic weight management[49, 50]. According to Mailhac et al., a survey conducted in 2022 from Denmark revealed that 1/3 of new semaglutide users did not have type 2 diabetes[50]. These benefits in rapid weight loss, however, may come with aesthetic consequences. Due to the significant weight reduction, the individual may be left with semaglutide-induced facial volume loss, the appearance of “sunken” eyes, and sagging skin resulting in the formation of jowls[51]. The areas mainly affected by this “semaglutide face” phenomenon are the cheeks, temples, neck, and periorbital regions[48]. However, this review aims to highlight that weight loss alone may not be solely responsible for “semaglutide face” but rather a contributing factor to a broader underlying mechanism affecting cutaneous elasticity.

Semaglutide is shown to reduce skin elasticity over time[52]. Elastin is an essential element of the skin that helps maintain its flexibility and capacity to return to its original shape, but it naturally decreases with age. The decline in elastin, along with a reduction in fat levels, leads to loose and sagging skin. Furthermore, there is altered proliferation and differentiation of adipose-derived stem cells (ADSCs), which play an important role in tissue repair[19]. GLP-1 agonists inhibit the proliferation of ADSCs, therefore inhibiting fibroblasts from regenerating the dermis, resulting in significant impairment of the skin quality[19]. All in all, the influence of GLP-1 agonists on the reduction of ADSCs and elastin potentially contributes to the "semaglutide face" phenomenon.

In review of the current literature, the characteristics of facial aging in individuals taking GLP-1 agonists manifest earlier than they would typically occur during the natural aging process. Further research is necessary to determine if the "semaglutide face" phenomenon is a direct biochemical effect of semaglutide on skin barrier components or simply a consequence of weight loss on facial appearance. Potential adjuvant treatments to minimize the appearance of volume loss may be necessary, including dermal fillers or surgical interventions. Furthermore, it remains unclear whether discontinuation of GLP-1 agonists and subsequent weight regain would benefit individuals experiencing "semaglutide face." Ultimately, patient education plays a crucial role in ensuring patients are well informed of the potential accelerated facial aging effects reported on semaglutide.

3. Conclusion

In our retrospective review of GLP-1 agonists, we reviewed published case reports detailing cited cases of cutaneous adverse effects of these new drug classes. While there are published studies on cutaneous neoplasms, alopecia, and facial aging as a result of GLP-1 agonists, we did not identify any published case reports featuring individual patients. Panniculitis and hypersensitivity reactions each had 10 individually cited cases, bullous pemphigoid had 5 reported cases, and morbilliform reactions had the fewest cited cases with 4. There were 29 individually cited patients with hypersensitivity reactions, morbilliform reactions, bullous pemphigoid and panniculitis; patients with these complications had an average age of 60.18. The average age of hypersensitivity reaction patients and bullous pemphigoid reaction patients cited in this study were both age 50. The average age of bullous pemphigoid patients was older at 69.2. Morbilliform reactions had the oldest average age of any cutaneous adverse reaction at 77. The patients with reported adverse cutaneous effects to GLP-1 agonists were also overwhelmingly white and male. Further research should be done to learn about the presentation of GLP-1 adverse effects in minority populations. In addition, there is a paucity of research on the presentation of cutaneous sequelae of GLP-1 inhibitors in patients with dark skin. Many dermatologic conditions present differently in patients who have higher amounts of melanin, and learning about the incidence and presentation of the disease in these patient populations would enhance the safety profile of GLP-1 agonists. Future research studies should additionally focus on comparing rates of adverse reactions to patients taking similar medications such as SGLT2i to learn how strongly use of this medication is associated with complications such as alopecia. Learning more about the immune response to PGLA's and factors that may cause different reactions in patients can help patients avoid atypical eosinophilic reactions such as panniculitis.

References

[1] Collins, M. K., Choudhary, S., Ho, J., Bunimovich, Y. L. (2021). *Bullous Pemphigoid Triggered by Liraglutide | MDedge*. Retrieved December 16, 2024, from https://mdedge.com/cutis/article/240500/mixed-topics/bullous-pemphigoid-triggered-liraglutide

[2] Rashmi Shetty, Fathima Thashreefa Basheer, Pooja Gopal Poojari, Girish Thunga, Viji Pulikkel Chandran, Leelavathi D. Acharya Adverse drug reactions of GLP-1 agonists: A systematic review of case reports. Diabetes & Metabolic Syndrome: Clinical Research & Reviews, Volume 16, Issue 3, 2022,

[3] Faurschou A, Pedersen J, Gyldenløve M, Poulsen SS, Holst JJ, Thyssen JP, Zachariae C, Vilsbøll T, Skov L, Knop FK. Increased expression of glucagon-like peptide-1 receptors in psoriasis plaques. Exp Dermatol. 2013 Feb;22(2):150-2. doi: 10.1111/exd.12081. PMID: 23362875.Pradhan R, Yu OHY, Platt RW, Azoulay L. Glucagon like peptide-1 receptor agonists and the risk of skin cancer among patients with type 2 diabetes: Population-based cohort study. Diabet Med. 2024;41:e15248. doi:10.1111/dme.15248.

[4] Samhani, C., Guerci, B., & Larose, C. (2024). Cutaneous hypersensitivity reaction to dulaglutide: A case report of an allergic reaction.

Diabetes & metabolism, *50*(5), 101552. https://doi.org/10.1016/j.diabet.2024.101552

[5] Kyriakos G, Diamantis E, Memi E, Elefsiniotis I. An Uncommon Case of Dulaglutide-Related Morbilliform Drug Eruption. Cureus. 2022 Jan 23;14(1):e21536. doi: 10.7759/cureus.21536.

[6] Moro, F., Fania, L., Sinagra, J. L. M., Salemme, A., & Di Zenzo, G. (2020). Bullous Pemphigoid: Trigger and Predisposing Factors. *Biomolecules*, *10*(10), 1432. https://doi.org/10.3390/biom1010 1432

[7] Salazar, C. E., Patil, M. K., Aihie, O., Cruz, N., & Nambudiri, V. E. (2024). Rare cutaneous adverse reactions associated with GLP-1 agonists: A review of the published literature. *Archives of Dermatological Research*, *316*(6), 248. https://doi.org/10.1007/s00403-024-029 69-3

[8] Desai, D. D., Sikora, M., Nohria, A., Bordone, L., Caplan, A. S., Shapiro, J., & Lo Sicco, K. I. (2024). GLP-1 agonists and hair loss: a call for further investigation. *International journal of dermatology*, *63*(9), 1128–1130. https://doi-org.rossuniversity.idm.oclc.org/10.1111/ijd.17246

[9] Carboni, A., Woessner, S., Martini, O., Marroquin, N. A., Waller, J. (2024). Natural Weight Loss or "Ozempic Face": Demystifying A Social Media Phenomenon. (n.d.). *JDDonline - Journal of Drugs in Dermatology*. Retrieved January 2, 2025, from https://jddonline-com.access.library.miami.edu/articles/ozempic-face-or-natural-weight-loss-demystifying-a-social-media-phenomenon-S15459616 24P7613 X/

[10] Dobrică, E. C., Banciu, M. L., Kipkorir, V., Khazeei Tabari, M. A., Cox, M. J., Simhachalam Kutikuppala, L. V., & Găman, M. A. (2022). Diabetes and skin cancers: Risk factors, molecular mechanisms and impact on prognosis. *World journal of clinical cases*, *10*(31), 11214–11225. https://doi.org/10.12998/wjcc.v10.i31.11214

[11] Kang, D. H., Kwon, S. H., Sim, W. Y., & Lew, B. L. (2024). Telogen Effluvium Associated With Weight Loss: A Single Center Retrospective Study. Annals of dermatology, 36(6), 384–388. https://doi.org/10.5021/ad.24. 043

[12] Panchaprateep R, Asawanonda P. Insulin-like growth factor-1: roles in androgenetic alopecia. Exp Dermatol. 2014 Mar;23(3):216-8. doi: 10.1111/exd.12339. PMID: 24499417.

[13] Desai DD, Sikora M, Nohria A, Bordone L, Caplan AS, Shapiro J, Lo Sicco KI. GLP-1 agonists and hair loss: a call for further investigation. Int J Dermatol. 2024 Sep;63(9):1128-1130. doi: 10.1111/ijd.17246. Epub 2024 May 13. PMID: 38741261.

[14] Tran, M. M., Mirza, F. N., Lee, A. C., Goldbach, H. S., Libby, T. J., & Wisco, O. J. (2024). Dermatologic findings associated with semaglutide use: A scoping review. *Journal of the American Academy of Dermatology*, *91*(1), 166–168. https://doi.org/10.1016/j.jaad.2024. 03. 02 1

[15] Moll, H., Frey, E., Gerber, P., Geidl, B., Kaufmann, M., Braun, J., Beuschlein, F., Puhan, M. A., & Yebyo, H. G. (2024). GLP-1 receptor agonists for weight reduction in people living with obesity but without diabetes: a living benefit-harm modelling study. *EClinical Medicine*, *73*, 102661. https://doi.org/10.1016/ j.eclinm.2024.102661

[16] Nakhla, M., Nair, A., Balani, P., Ujjawal, A., Arun Kumar, P., Dasari, M., Yukselen, Z., Bansal, K., Ganatra, S., & Dani, S. S. (2024). Risk of Suicide, Hair Loss, and Aspiration with GLP1-Receptor Agonists and Other Diabetic Agents: A Real-World Pharmacovigilance Study. *Cardiovascular drugs and therapy*, 10.1007/s10557-024-07613-w. Advance online publication. https://doi.org/10.1007/s10557-024-07613-w

[17] Rzepka PV, Kaffenberger JA. A CASE OF MORBILLIFORM DRUG ERUPTION TO DULAGLUTIDE. J Clin Aesthet Dermatol. 2020 Apr;13(4):13. Epub 2020 Apr 1. PMID: 33144906; PMCID: PMC7605389. (did not use for BP; maybe it was used for morbiliform?)

[18] Wen-Jun, L., Hai-Yan, W., Wei, L., Ke-Yu, W., & Rui-Ming, W. (2008). Evidence that geniposide abrogates norepinephrine-induced hypopigmentation by the activation of GLP-1R-dependent c-kit receptor signaling in melanocyte. *Journal of ethnopharmacology*, *118*(1), 154–158. https://doi.org/10.1016/j.jep. 2008.03.021

[19] Ridha, Z., Fabi, S. G., Zubar, R., & Dayan, S. H. (2024). Decoding the Implications of Glucagon-like Peptide-1 Receptor Agonists on Accelerated Facial and Skin Aging. *Aesthetic Surgery Journal*, *44*(11), NP809–NP818. https://doi.org/ 10.1093/asj/sjae132

[20] Ibrahim, S. S., Ibrahim, R. S., Arabi, B., Brockmueller, A., Shakibaei, M., & Büsselberg, D. (2024). The effect of GLP-1R agonists on the medical triad of obesity, diabetes, and cancer. *Cancer metastasis reviews*, *43*(4), 1297–1314. https://doi.org/10.1007/s10555-024-10192-9

[21] Nauck, M. A., Jensen, T. J., Rosenkilde, C., Calanna, S., Buse, J. B., & LEADER Publication Committee on behalf of the LEADER Trial Investigators (2018). Neoplasms Reported With Liraglutide or Placebo in People With Type 2 Diabetes: Results From the LEADER Randomized Trial. *Diabetes care*, *41*(8), 1663–1671. https://doi.org/10.2337/dc17-1825

[22] Pradhan, R., Yu, O. H. Y., Platt, R. W., & Azoulay, L. (2024). Glucagon like peptide-1 receptor agonists and the risk of skin cancer among patients with type 2 diabetes: Population-

based cohort study. *Diabetic medicine: a journal of the British Diabetic Association*, *41*(4), e15248. https://doi-org.rossuniversity.idm.oclc.org/10.1111/dme.15248

[23] Sun Y, Liu Y, Dian Y, Zeng F, Deng G, Lei S. Association of glucagon-like peptide-1 receptor agonists with risk of cancers-evidence from a drug target Mendelian randomization and clinical trials. Int J Surg. 2024 Aug 1;110(8):4688-4694. doi: 10.1097/JS9.0000000000001514. PMID: 38701500; PMCID: PMC11325911.

[24] Demoly, P., Adkinson, N. F., Brockow, K., Castells, M., Chiriac, A. M., Greenberger, P. A., Khan, D. A., Lang, D. M., Park, H. S., Pichler, W., Sanchez-Borges, M., Shiohara, T., & Thong, B. Y. (2014). International Consensus on drug allergy. *Allergy*, *69*(4), 420–437. https://doi.org/10.1111/all.12350

[25] Neel, NadaFouda & Ghobara, Yasser & Turkmani, Mohammed. (2019). Liraglutide-induced injection site reaction. *Journal of Dermatology and Dermatologic Surgery*. 23. 97. 10.4103/jdds.jdds_5_19.

[26] Yaneva, M., Handjieva-Darlenska, T., Kazandjieva, J., & Darlenski, R. (2023). Delayed type hypersensitivity injection site reaction and tolerance induction to liraglutide for the treatment of obesity. *JAAD case reports*, *38*, 100–101. https://doi.org/10.1016/j.jdcr.2023.06.010

[27] Steveling, E. H., Winzeler, B., & Bircher, A. J. (2014). Systemic Allergic Reaction to the GLP-1 Receptor Agonist Exenatide. *Journal of Pharmacy Technology*, *30*(5), 182–186. https://doi.org/10.1177/8755122514539462

[28] Pérez E, Martínez-Tadeo J, Callero A, Hernández G, Rodríguez-Plata E, García-Robaina JC. A case report of allergy to exenatide. J Allergy Clin Immunol Pract. 2014 Nov-Dec;2(6):822-3. doi: 10.1016/j.jaip.2014.05.011. Epub 2014 Jul 25. PMID: 25439386.

[29] Bianchi L, Ali Biglu Marash S, Malatesta N, Hansel K, Tramontana M, Stingeni L. Hypersensitivity to glucagon-like peptide-1 receptor agonists: a case of delayed urticaria-like rash to dulaglutide and literature review. *JEADV Clin Pract.* 2024; 3: 313–316. https://doi.org/10.1002/jvc2.255

[30] Shamriz, O., NaserEddin, A., Mosenzon, O., Sviri, S., & Tal, Y. (2019). Allergic Reaction to Exenatide and Lixisenatide but Not to Liraglutide: Unveiling Anaphylaxis to Glucagon-Like Peptide 1 Receptor Agonists. *Diabetes care*, *42*(9), e141–e142. https://doi.org/10.2337/dc19-0720

[31] Barroso, B., Gómez-López, A., Valverde-Monge, M., Betancor, D., de Las Heras, M., & Sastre, J. (2024). Hypersensitivity Reactions to the GLP-1 Receptor Agonists Liraglutide and Semaglutide: A Case Series. *Journal of investigational allergology & clinical immunology*, *34*(2), 133–135. https://doi.org/10.18176/jiaci.0932.

[32] Yeğit OO, Sarıbeyliler G, Karadağ P, Demir S, Gül N, Ünal D, Gelincik Akkor A. The first successful desensitization protocol in exenatide allergy: a case report. Allergy Asthma Clin Immunol. 2023 Jan 13;19(1):2. doi: 10.1186/s13223-023-00761-y. PMID: 36639791; PMCID: PMC9838064.

[33] Adame, J., & Cohen, P. R. (1996). Eosinophilic panniculitis: diagnostic considerations and evaluation. *Journal of the American Academy of Dermatology*, *34*(2 Pt 1), 229–234. https://doi.org/10.1016/s0190-9622(96)80117-4

[34] Boysen, N. C., & Stone, M. S. (2014). Eosinophil-rich granulomatous panniculitis caused by exenatide injection. *Journal of cutaneous pathology*, *41*(1), 63–65. https://doi.org/10.1111/cup.12246

[35] Andrés-Ramos, I., Blanco-Barrios, S., Fernández-López, E., & Santos-Briz, Á. (2015). Exenatide-Induced Eosinophil-Rich Granulomatous Panniculitis: A Novel Case Showing Injected Microspheres. *The American Journal of dermatopathology*, *37*(10), 801–802.

[36] Shan, S. J., & Guo, Y. (2014). Exenatide-induced eosinophilic sclerosing lipogranuloma at the injection site. *The American Journal of dermatopathology*, *36*(6), 510–512. https://doi.org/10.1097/DAD.0000000000000036

[37] Vidal CI, Chaudhry S, Burkemper NM. (2018). Exenatide-induced panniculitis: utility of the acid-fast stain to identify injected microspheres. *Am J Dermatopathol*, *40*(11):867–869. doi:10.1097/DAD.0000000000000952

[38] Ko JW, Park KD, Lee Y, Lee JH, Hong DK. (2020). Eosinophilic Panniculitis Following the Subcutaneous Injection of Exenatide Extended-Release. *Ann Dermatol*, *32*(3):230-232. https://doi.org/10.5021/ad.2020.32.3.230

[39] Williams, G., Kwan, E., Giraldo, C.N., Lincoln, M.R., & Lewin-Smith, M.R. (2020). Panniculitis at the Site of Injection: Infection or Foreign Body Reaction? *American Journal of Clinical Pathology*, *154*. https://doi.org/10.1093/ajcp/aqaa161.058

[40] Posso-Osorio, I., Vargas-Potes, C. J., Mejía, M., & Cañas, C. A. (2023). Eosinophil-related diseases during treatment with glucagon-like peptide one receptor (GLP-1 RA): a case report and review of the literature. *Clinical rheumatology*, *42*(9), 2501–2506. https://doi.org/10.1007/s10067-023-06612-w

[41] Riswold, K., & Flynn, V. (2018). Persistent injection site nodules from exenatide: Successful treatment with intralesional

triamcinolone. *JAAD case reports*, *4*(8), 830–832. https://doi.org/10.1016/j.jdcr.2018.06.009

[42] Zhu, C. S., Kwan, E. A., Williams, G. M., Lewin-Smith, M., Lincoln, M. S., & Lee, A. J. (2022). Exenatide-induced granulomatous panniculitis associated with poly(d,l-lactide-co-glycolide). *Journal of cutaneous pathology*, *49*(5), 496–499. https://doi.org/10.1111/cup.14193

[43] Eddie A. Kwan, Grant M. Williams, Michael R. Lewin-Smith, Mark S. Lincoln, Abigail J. Lee. (2021). 25734 Migratory panniculitis of the pannus. *Journal of the American Academy of Dermatology*, *85*(3). https://doi.org/10.1016/j.jaad.2021.06.295

[44] Fukuda, G., Yoshida, T., Hirayama, A., Umezawa, Y., & Takemoto, M. (2019). Dulaglutide-related bullous pemphigoid in a patient with type 2 diabetes: A case report. *Geriatrics & Gerontology International*, *19*(12), 1289–1290. https://doi.org/10.1111/ggi.13799

[45] Sonego, B., Zelin, E., Zalaudek, I., & di Meo, N. (2023). Bullous pemphigoid triggered by dulaglutide: A case report and a review of the literature. *Dermatology Reports*, *15*(3), 9676. https://doi.org/10.4081/dr.2023.9676

[46] Schwager, Z., Mikailov, A., & Lipworth, A. D. (2019). Comment on "Oral diabetes medications other than dipeptidyl peptidase-4 inhibitors are not associated with bullous pemphigoid: A Finnish nationwide case-control study" and a case report of glucagon-like peptide-1 receptor agonist–induced bullous pemphigoid. *Journal of the American Academy of Dermatology*, *80*(6), e189–e190. https://doi.org/10.1016/j.jaad.2019.01.086

[47] Burruss, C. P., Jones, J. M., & Burruss, J. B. (2021). Semaglutide-associated bullous pemphigoid. *JAAD Case Reports*, *15*, 107–109. https://doi.org/10.1016/j.jdcr.2021.07.027

[48] Montecinos, K., Kania, B., & Goldberg, D. J. (2024). Semaglutide "Ozempic" Face and Implications in Cosmetic Dermatology. *Dermatological Reviews*, *5*(5), e70003. https://doi.org/10.1002/der2.70003

[49] Haykal, D., Hersant, B., Cartier, H., & Meningaud, J.-P. (2024). The Role of GLP-1 Agonists in Esthetic Medicine: Exploring the Impact of Semaglutide on Body Contouring and Skin Health. *Journal of Cosmetic Dermatology*, *n/a*(n/a), e16716. https://doi.org/10.1111/jocd.16716

[50] Mailhac, A., Pedersen, L., Pottegård, A., Søndergaard, J., Mogensen, T., Sørensen, H. T., & Thomsen, R. W. (2024). Semaglutide (Ozempic®) Use in Denmark 2018 Through 2023 – User Trends and off-Label Prescribing for Weight Loss. *Clinical Epidemiology*, *16*, 307–318. https://doi.org/10.2147/CLEP.S456170

[51] Mansour, M., Hannawa, O. M., Yaldo, M. M., Nageeb, E. M., Chaiyasate, K. (2024). *The rise of "Ozempic Face": Analyzing trends and treatment challenges associated with rapid facial weight loss induced by GLP-1 agonists—ClinicalKey*. (n.d.). Retrieved January 2, 2025, from https://www-clinicalkey-com.access.library.miami.edu/#!/content/journal/1-s2.0-S1748681524004170

[52] Carboni, A., Woessner, S., Martini, O., Marroquin, N. A., Waller, J. (2024). Natural Weight Loss or "Ozempic Face": Demystifying A Social Media Phenomenon. (n.d.). *JDDonline - Journal of Drugs in Dermatology*. Retrieved January 2, 2025, from https://jddonline-com.access.library.miami.edu/articles/ozempic-face-or-natural-weight-loss-demystifying-a-social-media-phenomenon-S1545961624P7613X/

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