Poster ID – **P1469**

EADV CONGRESS 2026

SKIN AND MUCOSAL SIDE EFFECTS ASSOCIATED WITH GLP-1 RECEPTOR AGONISTS: A MULTINATIONAL CASE-CONTROL STUDY

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INTRODUCTION & OBJECTIVES

GLP-1 receptor agonists (GLP-1 RAs) are seeing widespread adoption for the treatment of type 2 diabetes (T2D) and obesity.

Their rapid spread has been accompanied by the emergence of dermatological signals, including the widely publicized phenomenon of 'Ozempic face' (facial hollowing linked to rapid loss of subcutaneous volume), as well as reports of skin rashes, dryness and mucosal manifestations from pharmacovigilance databases.

The data published to date are based primarily on case series or analyses lacking a comparator group, which makes it impossible to distinguish the effects specific to GLP-1 RAs from dermatological manifestations attributable to type 2 diabetes, obesity or weight loss itself.

The objective had to characterize the cutaneous, facial and mucosal effects in GLP-1 RA users, compared with a control group of patients with T2D and/or obesity who are not exposed to the treatment.

MATERIALS & METHODS

A multinational cross-sectional study (France, United States, Brazil, Mexico) including 575 GLP-1 RAs users and 1,329 controls (T2D and/or obesity, BMI > 30) with no exposure to GLP-1 RAs, recruited from a representative sample in each country. The assessment focused on skin problems, facial changes, skin reactions, dyschromia, as well as oral and mucosal manifestations. Weight loss was measured over a 3-month period. A stratified analysis of weight loss was performed.

RESULTS

GLP-1 RAs users (mean treatment duration 18.5 months; median 9 months) had significantly higher prevalences for: pruritus 60.7% vs 50.9% (OR = 1.49 [1.22-1.82], p<0.001), of which 26.3% were entirely facial oval modification 27.4% vs 8.2% (OR = 4.15 [3.05-5.65], p<0.001); skin texture changes 28.5% vs 11.2% (OR = 3.05 [2.48-3.76], p<0.001); nausea 42.6% vs 12.5% (OR = 5.22 [4.20-6.49], p<0.001); taste alteration 24.5% vs 8.3% (OR = 3.54 [2.46-5.10], p<0.001); overall oral health problems 52.3% vs 38.4% (OR = 1.76 [1.43-2.17], p<0.001); taste alteration 24.5% vs 8.3% (OR = 3.54 [2.46-5.10], p<0.001).

At least one skin-related adverse event was reported by 86.8% of users vs 72.1% of controls (p=0.002). Paradoxically, at least one dermatological manifestation was reported by 86.8% of GLP-1 Ras users, possibly linked to metabolic improvement despite facial wasting.

In a subgroup analysis restricted to patients who had lost weight, the differences persisted (skin rash 51.4% vs 20.1%, ×2.6; facial hollowing 20.9% vs 8.5%, ×2.5; confirmed change in taste), demonstrating that weight loss alone does not explain these manifestations.

CONCLUSIONS

This large-scale case-control study, featuring an appropriate T2D/obese control group, highlights a distinct cutaneous-mucosal profile associated with GLP-1 RAs: rashes, facial remodelling (sunken cheeks, altered facial contours), cutaneous xerosis, oral-dental disorders and taste disturbance. The persistence of these associations after stratification by weight loss suggests specific mechanisms, independent of weight reduction — possibly linked to direct effects on skin and mucosal hydration, on the redistribution of subcutaneous tissue, and on skin homeostasis. Routine dermatological monitoring should be incorporated into prescribing protocols. Longitudinal studies are needed to establish temporal relationships, pathophysiological mechanisms and reversibility upon discontinuation of treatment.

TABLES & FIGURES

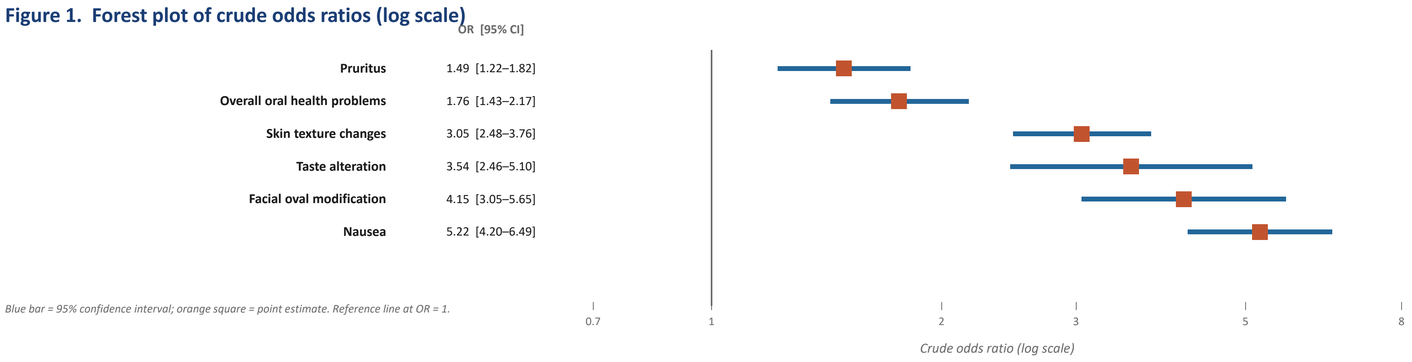
Table 1. Prevalence and crude odds ratios of skin and mucosal manifestations

GLP-1 RA users (n = 575) vs controls with type 2 diabetes and/or obesity, BMI > 30 (n = 1,329)

Manifestation	GLP-1 RA users (n = 575)	Controls (n = 1,329)	OR	95% CI	p-value
At least one skin-related adverse event	86.8%	72.1%	—	—	0.002
Pruritus	60.7%	50.9%	**1.49**	1.22 – 1.82	<0.001
Facial oval modification	27.4%	8.2%	**4.15**	3.05 – 5.65	<0.001
Skin texture changes	28.5%	11.2%	**3.05**	2.48 – 3.76	<0.001
Nausea	42.6%	12.5%	**5.22**	4.20 – 6.49	<0.001
Taste alteration	24.5%	8.3%	**3.54**	2.46 – 5.10	<0.001
Overall oral health problems	52.3%	38.4%	**1.76**	1.43 – 2.17	<0.001

OR = crude odds ratio; CI = confidence interval. Comparison group: type 2 diabetes and/or obesity (BMI > 30), unexposed to GLP-1 RAs.

Figure 1. Forest plot of crude odds ratios (log scale)



Blue bar = 95% confidence interval; orange square = point estimate. Reference line at OR = 1.

Table 2. Subgroup — patients with confirmed weight loss

Effects persist when the analysis is restricted to patients who actually lost weight — arguing against weight loss alone as the sole mechanism

Manifestation	GLP-1 RA users	Controls	Fold change
Skin rash	51.4%	20.1%	**× 2.6**
Facial hollowing	20.9%	8.5%	**× 2.5**

Key point: the between-group differences observed in the overall population persist in the weight-loss subgroup, suggesting that weight loss alone does not fully explain the cutaneous and facial manifestations observed under GLP-1 RA therapy.

Presented at the European Academy of Dermatology and Venereology Annual Congress, 30 September 2026, Vienna , Austria

This project was carried out with institutional support from Laboratoire Ducray