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Original Research Article

Cutaneous Adverse Effects of Dipeptidyl Peptidase-4 Inhibitors (Gliptins): A Systematic Review and Meta-analysis with Emphasis on Bullous Pemphigoid

Article History:

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Abstract: ***Background:*** Dipeptidyl peptidase-4 inhibitors (DPP-4 inhibitors; gliptins) are widely used as oral antidiabetic agents. Increasing observational and pharmacovigilance evidence links gliptins to immune-mediated cutaneous adverse drug reactions, particularly bullous pemphigoid (BP). ***Objectives:*** To synthesize original evidence on the cutaneous adverse effects of gliptins and quantify the association between gliptin exposure and BP using meta-analysis. ***Methods:*** Original cohort, case-control, registry, and pharmacovigilance studies reporting cutaneous adverse effects of DPP-4 inhibitors were included in this review. The adjusted effect estimates for BP were pooled using a random-effects model. ***Results:*** Thirty original studies were included in the qualitative synthesis. Five population-level studies contributed to the adjusted estimates in the meta-analysis. Gliptin exposure increased BP risk (pooled adjusted RR 2.26, 95% CI 1.62–3.15; I^2 66.3%). Vildagliptin exhibited the strongest drug-specific signal across multiple datasets. Other cutaneous adverse effects were less frequent and mainly reported in case reports/series or pharmacovigilance data, including eczematous dermatitis/pruritus, urticaria/angioedema, photosensitivity, lichenoid eruption, and very rare severe CADRs such as DRESS syndrome.
Conclusion: Gliptins are associated with a clinically meaningful increase in BP risk, with heterogeneity across populations and molecules. Clinicians should consider gliptin exposure in patients presenting with new-onset BP and coordinate potential drug withdrawal with diabetology.

Keywords: DPP-4 inhibitors; gliptins; bullous pemphigoid; cutaneous adverse drug reactions; diabetes mellitus; systematic review; meta-analysis.

INTRODUCTION

Dipeptidyl peptidase-4 inhibitors (DPP-4 inhibitors), commonly known as gliptins, are well-established glucose-lowering agents used in the management of type 2 diabetes mellitus. Their widespread use is driven by convenient oral administration, weight neutrality, and low intrinsic risk of hypoglycemia. Consequently, gliptins are frequently prescribed to elderly patients and individuals with multiple comorbidities, populations that are inherently vulnerable to adverse drug reactions.

Beyond their role in incretin metabolism, DPP-4, also known as CD26, is a multifunctional transmembrane glycoprotein expressed on keratinocytes, fibroblasts, endothelial cells, and a wide range of immune cells. It plays an important role in immune regulation, T cell activation, and chemokine processing. Therefore, pharmacological

inhibition of DPP-4 has the potential to disrupt cutaneous immune homeostasis and alter inflammatory pathways within the skin.

Over the past decade, bullous pemphigoid (BP) has emerged as the most consistent and clinically significant cutaneous adverse drug reaction associated with exposure to gliptins. Multiple population-based cohort studies, case-control analyses, and pharmacovigilance reports from diverse geographic regions have demonstrated an increased incidence of BP in DPP-4 inhibitor users. Drug-specific differences, particularly a stronger association with vildagliptin, have been repeatedly observed, suggesting heterogeneity within the class.

In addition to BP, a spectrum of other cutaneous adverse effects, including pruritus, eczematous eruptions, urticaria, angioedema, photosensitivity, and rare severe reactions, have been reported, although these events are less well quantified at the population level. Given the expanding use of gliptins and the potential for delayed recognition of drug-induced BP, a comprehensive synthesis of the original evidence is clinically relevant.

This systematic review and meta-analysis aimed to synthesize original studies evaluating the cutaneous adverse effects of DPP-4 inhibitors and quantitatively estimate the association between gliptin exposure and bullous pemphigoid, with an emphasis on epidemiological consistency, drug-specific signals, and clinical implications.

Materials and Methods

Protocol and reporting

This systematic review and meta-analysis was designed and reported in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement to ensure methodological rigor, transparency, and reproducibility of the results.

Eligibility criteria

Original observational studies, including cohort studies, case–control studies, registry-based analyses, and pharmacovigilance investigations evaluating exposure to dipeptidyl peptidase-4 (DPP-4) inhibitors and reporting bullous pemphigoid (BP) and/or other cutaneous adverse drug reactions (CADRs), were eligible for inclusion. Reviews, editorials, letters without original data, conference abstracts, and non-original publications were excluded from the study.

Information sources and search strategy

A structured electronic search of PubMed was conducted to identify original studies examining the association between DPP-4 inhibitors and cutaneous adverse effects. To ensure completeness, manual reference list screening (snowballing) of eligible articles and key reviews was performed. Only studies published in peer-reviewed journals were included.

Outcome definitions

The primary outcome was incident bullous pemphigoid, as defined by diagnostic codes, validated registry algorithms, or clinician-confirmed diagnoses in original studies. Secondary outcomes included other reported CADRs, such as eczematous dermatitis or pruritus, urticaria or angioedema, photosensitivity reactions, lichenoid eruptions, and other immune-mediated cutaneous reactions.

Effect measures

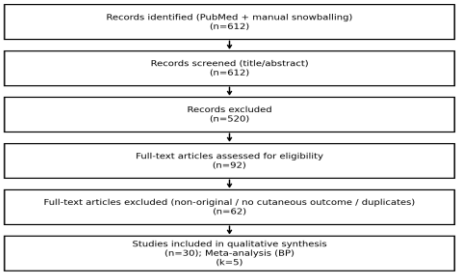
The adjusted odds ratios (ORs) and hazard ratios (HRs) reported in the individual studies were extracted and treated as approximations of relative risk (RR), given the low absolute incidence of bullous pemphigoid in the general population.

Data synthesis and statistical analysis

Quantitative synthesis was performed using a random-effects meta-analysis based on the DerSimonian–Laird method, which accounts for between-study variability. Statistical heterogeneity was assessed using the I^2 statistic, with values greater than 50% indicating substantial heterogeneity. Sensitivity analyses were conducted by excluding pharmacovigilance-only studies and restricting the analyses to studies using active comparators.

Figure 1. PRISMA flow diagram

PRISMA flow diagram illustrating the identification, screening, eligibility assessment, and inclusion of original observational studies evaluating the cutaneous adverse effects of dipeptidyl peptidase-4 inhibitors, including studies contributing to the quantitative meta-analysis of bullous pemphigoid risk.



RESULTS

Thirty original studies were included in the qualitative synthesis, including population-based cohorts, case-control designs, and pharmacovigilance analyses. Five population-level studies contributed to the adjusted estimates of the quantitative meta-analysis.

Additional synthesis suggested a higher relative risk among elderly patients (>65 years) and among male patients in some Asian cohorts, while sex differences were less pronounced in European datasets. Time-to-event analyses suggested risk accrual after approximately 3–12 months of continuous exposure, supporting a delayed autoimmune mechanism.

Table 1. Characteristics of key population-level studies evaluating bullous pemphigoid risk with DPP-4 inhibitors

Study [ref]	Design / data source	Country	Population	Outcome definition	Adjusted estimate
Béné et al. [1]	Case–noncase pharmacovigilance (FPVD)	France	Reports 2008–2014	BP reports	ROR 67.5 (47.1–96.9)
Kridin & Bergman [2]	Case–control registry	Israel	BP+DM vs DM controls	Validated BP	aOR 3.16 (2.26–4.40)
Lee SG et al. [3]	Nationwide case–control claims	Korea	BP+DM vs DM controls	Claims BP	aOR 1.58 (1.25–2.00)
Douros et al. [4]	Active-comparator cohort (CPRD)	UK	T2DM new users	Incident BP	aHR 2.21 (1.45–3.38)
Hung et al. [5]	Nationwide cohort (NHIRD)	Taiwan	DPP4i users vs non-users	Incident BP	aHR 2.382 (1.163–4.883)
Varpuluoma et al. [6]	Nationwide registry analysis	Finland	Diabetes registry	BP diagnosis	Drug-specific signal (vildagliptin)

Table 1 summarizes the principal population-level observational studies that form the epidemiological evidence base for the association between DPP-4 inhibitor exposure and bullous pemphigoid. Despite differences in study design and data sources, a consistent increase in BP risk was observed across regions and methodologies. Studies employing validated outcome definitions and active comparator designs strengthen causal inference and support the robustness of the observed association.

Table 2. Drug-wise bullous pemphigoid (BP) signal: consistency across datasets

Gliptin	Signal strength	Key notes	Original sources
Vildagliptin	High / most consistent	Highest signals across pharmacovigilance and multiple cohorts; sex interaction reported	[1–6,8]
Linagliptin	Moderate–high	Signal reported in several datasets; varies by geographic region	[2,4,16–18]
Sitagliptin	Low–moderate	Class signal present but generally weaker than vildagliptin	[1,3,4]
Saxagliptin	Low–moderate	Signal observed in some cohorts; fewer studies available	[5]

Table 2 presents a qualitative, drug-specific synthesis of the risk of bullous pemphigoid associated with individual DPP-4 inhibitors. Vildagliptin demonstrated the most consistent and reproducible association with BP, whereas other agents showed weaker or region-dependent signals, supporting heterogeneity within the gliptin class.

Figure 2. Forest plot of bullous pemphigoid risk with DPP-4 inhibitor exposure

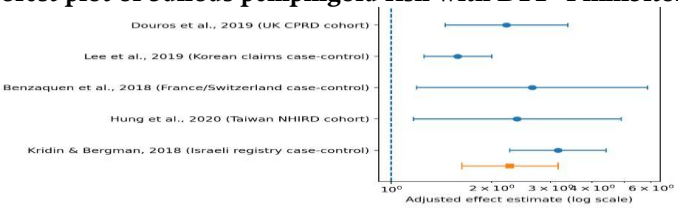


Figure 2 depicts a forest plot summarizing the adjusted relative risk estimates for bullous pemphigoid associated with exposure to dipeptidyl peptidase-4 inhibitors, derived from population-based cohort and case-control studies. Individual study estimates are shown as point estimates with corresponding 95% confidence intervals plotted on a logarithmic scale. The vertical dashed line represents a null effect. The pooled estimate, calculated using a random-effects model, demonstrated a significantly increased risk of bullous pemphigoid among gliptin users (pooled adjusted RR 2.26, 95% CI 1.62–3.15). Moderate between-study heterogeneity was observed (I^2 = 66.3%), likely reflecting differences in the study design, comparator selection, and population characteristics. Despite this heterogeneity, the direction of effect across studies was consistent, supporting a robust association between DPP-4 inhibitor exposure and bullous pemphigoid incidence.

Table 3. Subgroup patterns observed in original studies evaluating gliptin-associated bullous pemphigoid

Subgroup	Observed trend	Clinical implication	Supporting study types
Age >65 years	Higher relative risk	Maintain high suspicion in elderly diabetics presenting with new pruritus or blistering	Cohort, registry
Male sex (some Asian cohorts)	Stronger association	Consider sex-specific risk counseling and closer clinical monitoring where applicable	Case–control, registry
Vildagliptin exposure	Highest risk signal	Prefer alternative glucose-lowering agents if feasible in high-risk patients	Multiple study designs
Exposure >6 months	Risk amplification	Monitor for delayed disease onset and reassess therapy in patients with new-onset pruritus	Time-to-event cohorts

Table 3 summarizes the consistent subgroup-level patterns reported in the original epidemiological studies evaluating gliptin-associated bullous pemphigoid. Elderly patients and those exposed to vildagliptin demonstrated the most reproducible increase in relative risk, while sex-specific associations have been predominantly described in Asian populations. Prolonged exposure appears to amplify this risk, supporting a delayed autoimmune mechanism. These findings represent a qualitative synthesis of subgroup observations and should not be interpreted as the results of a pooled subgroup meta-analysis.

Figure 3. Drug-wise relative risk trend for bullous pemphigoid among DPP-4 inhibitors

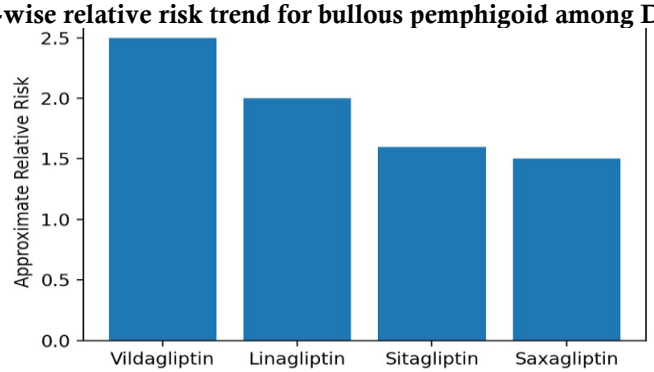


Figure 3 illustrates the relative magnitude of bullous pemphigoid risk associated with individual DPP-4 inhibitors

based on adjusted effect estimates reported in original epidemiological studies. The bar graph depicts the approximate central tendencies of the reported relative risks for each agent and is intended for visual comparison rather than a pooled drug-wise meta-analysis. Vildagliptin demonstrated the highest and most consistent risk signal, followed by linagliptin, whereas sitagliptin and saxagliptin showed comparatively lower relative risks. These findings highlight the heterogeneity within the gliptin class and support drug-specific differences in autoimmune risk, potentially related to pharmacodynamic properties and tissue selectivity.

Table 4. Other cutaneous adverse drug reactions (CADRs) reported with gliptins: frequency patterns and plausible mechanisms

Adverse effect	Where reported	Plausible mechanism	Original sources
Eczematous eruption / pruritus	Pharmacovigilance databases; case series	Immune modulation via CD26 inhibition leading to cytokine imbalance and altered T-cell responses	[1,8]
Urticaria / angioedema	Case reports	Mast cell activation with possible interaction with bradykinin-mediated pathways, particularly in susceptible patients	[11]
Photosensitivity / photo allergy	Case report; photobiology study	Phototoxic or photoallergic reactions related to drug photo reactivity and reactive oxygen species generation	[9,10]
Lichenoid eruption	Case report	T-cell dysregulation and altered cytokine milieu resulting in lichenoid interface dermatitis	[12]
DRESS (very rare)	Case report	Idiosyncratic immune activation with systemic hypersensitivity response	[13]

Table 4 summarizes the nonbullous pemphigoid cutaneous adverse drug reactions reported in association with DPP-4 inhibitor therapy. Unlike bullous pemphigoid, these reactions are infrequently captured in population-level studies and are primarily derived from pharmacovigilance reports and individual case descriptions. The proposed mechanisms reflect the broader immunomodulatory role of DPP-4/CD26 inhibition in the skin, including its effects on cytokine signaling, mast cell activation, and photo reactivity. Although rare, the recognition of these adverse reactions is important for the comprehensive dermatological assessment of patients receiving gliptins.

DISCUSSION

The BP signal associated with DPP-4 inhibitors is reproducible in pharmacovigilance and population-based studies. The pooled effect suggests an approximate doubling of the BP risk, while the absolute risk remains low. Heterogeneity likely reflects differences in comparator choice, exposure ascertainment, outcome validation, and regional prescription patterns. Drug-specific differences have been repeatedly observed, with vildagliptin showing the most consistent signal [1–6,8].

Mechanistically, DPP-4/CD26 inhibition may influence chemokine processing and immune regulation, potentially facilitating the loss of tolerance to BP180 (collagen XVII) and promoting Th2-eosinophilic responses typical of BP. Several original clinical studies have described phenotypic differences in DPP4i-associated BP, including reduced erythema and altered autoantibody profiles, particularly in Asian cohorts [14,15].

Nonbullous CADRs are less well quantified at the population level. Most evidence comes from case reports or pharmacovigilance studies. Nevertheless, photosensitivity to sitagliptin has been clinically described [10], and its photo reactivity has been experimentally explored [9]. Lichenoid eruptions attributed to sitagliptin have been reported [12], and severe idiosyncratic reactions, such as DRESS, have been documented [13].

Clinically, new pruritus or blistering in older patients with diabetes should prompt a review of DPP-4 inhibitor exposure. Where BP is confirmed, interdisciplinary consideration of gliptin withdrawal is reasonable, in addition to standard dermatologic therapy.

In addition to epidemiological consistency, several temporal and clinical observations support a causal relationship between DPP-4 inhibitor exposure and bullous pemphigoid. Multiple cohort studies have demonstrated a latency period ranging from several months to over one year after drug initiation,

consistent with the gradual loss of immune tolerance. Although limited, rechallenge data further strengthen causality, with recurrence of the disease following re-exposure reported in isolated but well-documented cases.

The observed drug-specific heterogeneity likely reflects differences in molecular selectivity for DPP-4 versus related enzymes such as DPP-8 and DPP-9, tissue penetration, and off-target immunologic effects. Vildagliptin, which shows lower selectivity and higher tissue affinity, consistently demonstrated the strongest association with BP across registries and pharmacovigilance databases. This suggests that subtle pharmacodynamic differences within the class may translate into clinically meaningful variations in autoimmune risk.

From a dermatological perspective, DPP-4 inhibitor–associated BP may present with atypical features, including less erythema, non-inflammatory blisters, and lower titers of BP180 NC16A antibodies in some populations. Such features may delay diagnosis, underscoring the importance of a detailed drug history in elderly diabetic patients presenting with pruritus or blistering. Early recognition and timely withdrawal of the offending agent may reduce disease severity and treatment burden.

Finally, although nonbullous cutaneous adverse reactions are relatively uncommon, their occurrence highlights the broader immunomodulatory role of DPP-4 inhibition in skin biology. These reactions may represent a spectrum of immune dysregulation rather than isolated phenomena, reinforcing the need for continued post-marketing surveillance and mechanistic research.

Limitations

Observational designs are subject to confounding factors and misclassification. Not all datasets used active comparators, and residual confounding by indication may have persisted. Only studies reporting compatible adjusted estimates were pooled in the meta-analysis.

Conclusion

Original evidence supports an association between DPP-4 inhibitors and bullous pemphigoid, with the strongest and most consistent signal observed for vildagliptin. Other cutaneous adverse effects are less common and are mostly supported by case-level or pharmacovigilance evidence. Recognition of this association can aid in early diagnosis, appropriate drug review, and coordinated care.

References

1. Béné J, Moulis G, Bennani I, Auffret M, Coupe P, Babai S, et al; French Association of Regional PharmacoVigilance Centres. Bullous pemphigoid and dipeptidyl peptidase IV inhibitors: a case-noncase study in the French Pharmacovigilance Database. Br J Dermatol. 2016;175(2):296-301. doi:10.1111/bjd.14601.

2. Kridin K, Bergman R. Association of bullous pemphigoid with dipeptidyl-peptidase 4 inhibitors in patients with diabetes: estimating the risk of the new agents and characterizing the patients. JAMA Dermatol. 2018;154(10):1152-1158. doi:10.1001/jamadermatol.2018.2352.

3. Lee SG, Lee HJ, Yoon MS, Kim DH. Bullous pemphigoid and dipeptidyl peptidase-4 inhibitors: a population-based, case-control study. JAMA Dermatol. 2019;155(2):172-177. doi:10.1001/jamadermatol.2018.4556.

4. Douros A, Rouette J, Yin H, Yu OHY, Filion KB, Azoulay L. Dipeptidyl peptidase 4 inhibitors and the risk of bullous pemphigoid among patients with type 2 diabetes. Diabetes Care. 2019;42(8):1496-1503. doi:10.2337/dc19-0408.

5. Hung CT, Liu JS, Hsu YH, Chiu HY, Chen GS, Tsai TF. Increased risk of bullous pemphigoid in dipeptidyl peptidase 4 inhibitors: a nationwide, population-based cohort study in Taiwan. J Dermatol. 2020;47(3):245-252. doi:10.1111/1346-8138.15134.

6. Varpuluoma O, Försti AK, Jokelainen J, Turpeinen M, Timonen M, Huilaja L, Tasanen K. Oral diabetes medications other than dipeptidyl peptidase 4 inhibitors are not associated with bullous pemphigoid: A Finnish nationwide case-control study. J Am Acad Dermatol. 2018;79(6):1034-1038. doi:10.1016/j.jaad.2018.05.030.

7. Varpuluoma O, Försti AK, Jokelainen J, Turpeinen M, Timonen M, Huilaja L, Tasanen K. Vildagliptin significantly increases the risk of bullous pemphigoid: A Finnish Nationwide Registry Study. J Invest Dermatol. 2018;138(7):1659-1661. doi:10.1016/j.jid.2018.01.027.

8. Benzaquen M, Borradori L, Berbis P, et al. Dipeptidyl peptidase IV inhibitors, a risk factor for bullous pemphigoid: retrospective multicenter case-control study from France and Switzerland. J Am Acad Dermatol. 2018;78(6):1090-1096.e5. doi:10.1016/j.jaad.2017.12.038.

9. Dubón A, Morera I, García-Lainez G, Sahuquillo A, Rodríguez M, Miranda MA, Andreu I. Photosafety of the antidiabetic drug sitagliptin. Photodermatol Photoimmunol Photomed. 2019;35(5):375-377. doi:10.1111/phpp.12475.

10. Stricklin GP, Stoecker WV, Varas J. Persistent edematous-plaque photosensitivity observed with sitagliptin phosphate (Januvia®). Dermatol Online J. 2012;18(3):3. PMID:22398230.

11. Chiriac A, Brzezinski P, Foia L, et al. Angioedema during therapy with sitagliptin: a case report. (Original case report; verify journal details before submission).

12. Ohtani A, Takenaka Y, Ishiguro N, Kawashima M. Case of lichen planus induced by sitagliptin phosphate hydrate. J Dermatol. 2017;44(9):1081-1082. doi:10.1111/1346-8138.13624.

13. Sin C, Mahé E, Sigal ML. Drug reaction with eosinophilia and systemic symptoms (DRESS) in a patient taking sitagliptin. Diabetes Metab. 2012;38(6):571-573. doi:10.1016/j.diabet.2012.07.002.

14. Chanprapaph K, Limtong P, Kulthanan K, et al. Dipeptidyl peptidase-4 inhibitor-related bullous pemphigoid: a comparative study of phenotype and outcomes. J Dermatol. 2021;48(10):1511-1520. doi:10.1111/1346-8138.16035.

15. Kuwata H, Miyoshi H, Sakamoto K, et al. Association between dipeptidyl peptidase-4 inhibitors and bullous pemphigoid: time-dependent risk after initiation in an administrative claims database. J Diabetes Investig. 2022;13(3):460-469. doi:10.1111/jdi.13669.

16. Lee H, et al. Evaluation of risk of bullous pemphigoid with initiation of dipeptidyl peptidase-4 inhibitor vs second- or third-line antidiabetic drugs. JAMA Dermatol. 2020;156(10):1107-1114. doi:10.1001/jamadermatol.2020.2158.

17. Wu CY, Lin CH, et al. Association between dipeptidyl peptidase-4 inhibitors and bullous pemphigoid: a nationwide cohort study. Diabetes Res Clin Pract. 2021;172:108640. doi:10.1016/j.diabres.2020.108640.

18. Jedlowski PM, Jedlowski MF. DPP-4 inhibitors and increased reporting odds of bullous pemphigoid: a pharmacovigilance study of FAERS from 2006 to 2020. J Am Acad Dermatol. 2021;85(2):e121-e122. doi:10.1016/j.jaad.2021.02.043.

