JAMA Dermatology | Original Investigation

Association of Bullous Pemphigoid With Dipeptidyl-Peptidase 4 Inhibitors in Patients With Diabetes

Estimating the Risk of the New Agents and Characterizing the Patients

Khalaf Kridin, MD; Reuven Bergman, MD

IMPORTANCE The association of bullous pemphigoid (BP) with the use of dipeptidyl-peptidase 4 (DPP-4) inhibitors among patients with diabetes has recently emerged. The risk of developing BP during treatment with new DPP-4 inhibitor agents like linagliptin is yet to be established. The clinical features and the prognostic outcomes of patients with DPP-4 inhibitor–associated BP are yet to be established.

OBJECTIVES Primarily to estimate the association between DPP-4 inhibitor exposure and the development of BP, and secondarily to characterize the clinical features and history of patients with DPP-4 inhibitor–associated BP.

DESIGN, SETTING, AND PARTICIPANTS A retrospective case-control study of the intake of different DPP-4 inhibitor agents and metformin and occurrence of BP among patients with diabetes in a tertiary care referral center for autoimmune bullous diseases in northern Israel. Included were 82 consecutive patients with diabetes and immunopathologically validated BP diagnosed between January 1, 2011, and December 31, 2017, and 328 age-, sex-, and ethnicity-matched control participants with diabetes but without BP.

MAIN OUTCOMES AND MEASURES Patients with diabetes and BP and exposure to DPP-4 inhibitors were followed up for a median of 2.0 years and compared with other patients with diabetes and BP who were not exposed to DPP-4 inhibitors regarding clinical and immunological features, laboratory analyses, treatments, and clinical outcomes.

RESULTS Eighty-two patients with BP and 328 age- and sex-matched control participants were enrolled; mean (SD) age, 79.1 (9.1) years; and 44 patients were female (53.7%). Overall, DPP-4 inhibitor intake was associated with a 3-fold increased risk for BP (adjusted odds ratio [OR], 3.2; 95% CI, 1.9-5.4). The adjusted ORs for vildagliptin and linagliptin were 10.7 (95% CI, 5.1-22.4) and 6.7 (95% CI, 2.2-19.7), respectively. The association of DPP-4 inhibitor use with BP was independent of the use of metformin and was stronger among male (OR, 4.46; 95% CI, 2.11-9.40) than female (OR, 1.88; 95%, CI 0.92-3.86) patients and strongest in patients younger than 70 years (OR, 5.59; 95% CI, 1.73-18.01). Patients with DPP-4 inhibitor–associated BP presented with higher mucosal involvement (22.2% vs 6.5%; $P = .04$) and lower mean (SD) peripheral eosinophil counts (399.8 [508.0] vs 1117.6 [1847.6] cells/μL; $P = .01$) than those with BP who had not been exposed to DPP-4 inhibitor. Discontinuation of DPP-4 inhibitor treatment was followed by improved clinical outcomes.

CONCLUSIONS AND RELEVANCE Vildagliptin and, to a lesser extent, linagliptin are associated with an increased risk of BP. This may partly explain the increasing incidence of BP in Israel. Discontinuation of DPP-4 inhibitor treatment in patients with diabetes should be considered when BP is diagnosed.

JAMA Dermatol. doi:10.1001/jamadermatol.2018.2352
Published online August 8, 2018.

Supplemental content

Author Affiliations: Department of Dermatology, Rambam Health Care Campus, Haifa, Israel (Kridin, Bergman); Rappaport Faculty of Medicine, Technion-Israel Institute of Technology, Haifa, Israel (Bergman).

Corresponding Author: Khalaf Kridin, MD, Department of Dermatology, Rambam Health Care Campus, POB 9602, Haifa 31096, Israel (dr_kridin@hotmail.com).

Recent observational studies have reported increased incidence of bullous pemphigoid (BP), between 1.9-fold and 4.3-fold, in the past 2 decades.[1-5] One of the putative explanations for this rise is the increased use of some drugs reported to increase the risk of BP in the elderly.[2]

An increasing body of evidence suggests that dipeptidyl-peptidase 4 (DPP-4) inhibitors, oral agents used to treat type 2 diabetes mellitus, may be implicated in the development of BP. The knowledge regarding the association between DPP-4 inhibitor exposure and BP is based mainly on case reports[6-13] and national pharmacovigilance database analyses.[14,15] Two controlled observational studies aimed to investigate this association in depth, but they were underpowered to estimate the risk of developing BP during treatment with newer DPP-4 inhibitor agents like linagliptin.[16,17] The clinical, immunologic, and histologic features of patients with DPP-4 inhibitor-associated BP is yet to be established.

The primary end point of the current study is to assess the association between DPP-4 inhibitor intake and the development of BP, shedding light on the specific risk of each of the DPP-4 inhibitor agents, including linagliptin. The secondary end point was to characterize the subgroup of patients with DPP-4 inhibitor-associated BP compared with other patients with diabetes and BP and to estimate the clinical course in this subgroup.

Key Points

Question Does the use of dipeptidyl-peptidase 4 (DPP-4) inhibitors increase the risk for bullous pemphigoid (BP) in patients with diabetes, and what are the clinical characteristics and outcomes of patients with DPP-4 inhibitor–associated BP?

Findings In this case-control study of 82 patients with diabetes and BP and 328 control participants with diabetes but without BP, use of the DPP-4 inhibitors vildagliptin and, to a lesser extent, linagliptin was associated with increased risk for BP. Patients with diabetes and DPP-4 inhibitor–associated BP have higher mucosal involvement and lower eosinophil counts than those with diabetes and BP but without exposure to DPP-4 inhibitor.

Meaning Discontinuation of treatment with DPP-4 inhibitor should be considered for patients with diabetes when BP is diagnosed; the recently increased use of DPP-4 inhibitors may explain in part the increasing incidence of BP.

Methods

Design and Study Population

The study was designed as a case-control study. The case group included all patients with diabetes who received a new diagnosis of BP between January 1, 2011, and December 31, 2017, at Rambam Health Care Campus, Haifa, Israel. The inclusion criteria for case patients and the strategy of therapy are detailed in the eAppendix in the Supplement.

The control group consisted of patients with diabetes but without BP who were admitted for laparoscopic hernia repair and excision of nonmelanoma skin lesions in our center between the years 2011 and 2017. The control group was randomly selected and frequency matched to cases by age, sex, and year of diagnosis. Four control participants were randomly selected for each case patient. The medical files of both case patients and controls were reviewed manually to determine DPP-4 inhibitor exposure. This retrospective, noninterventional study was approved by the institutional ethical board of Rambam Health Care Campus, waiving patient written informed consent.

Definition of Outcomes

Clinical outcomes were defined in accordance with the consensus of the management of BP recommended by an international panel of experts.[18] Disease severity was categorized, based on the clinical description, as either "mild or moderate" and "severe."[19,20] Eosinophil count and other hematological parameters of the cases were recorded on admission of patients with new-onset BP (before the initiation of any systemic therapy).

Statistical Analysis

All continuous parameters are expressed as mean (SD) values. Categorical variables are expressed as proportions. Comparisons of percentages between different patient groups were carried out using the χ^2 test. Logistic regression was then used to calculate the odds ratio (OR) and 95% confidence interval (CI) to compare cases and controls with respect to the frequency of DPP-4 inhibitor exposure. Homogeneity of ORs across strata was tested using the Breslow-Day and Tarone tests. $P < .05$ was considered significant. All statistical analysis was performed using SPSS software, version 22 (IBM Corporation).

Results

Demographic Characteristics of the Study Participants

Eighty-two patients with BP and 328 age- and sex-matched control participants were enrolled in the present study. The mean (SD) age at presentation was 79.1 (9.1) years, and 44 patients were female (53.7%). The demographic features of the case and control groups were comparable (**Table 1**).

DPP-4 Inhibitor in Case Patients and Controls

Thirty-six (44%) case patients with BP were treated with DPP-4 inhibitor at the onset of BP, compared with 71 (21.6%) control participants at the time of their enrollment ($P < .001$). Among cases, the most frequently prescribed DPP-4 inhibitor was vildagliptin, being administered to 24 case patients (29%) and 14 (4.3%) control participants ($P < .001$). Linagliptin was more common among case patients (n = 9; 11%) than among controls (n = 6; 4.7%; $P = .03$). Interestingly, use of sitagliptin was less common among case patients (n = 6; 7%) than among controls (n = 51; 15.5%) ($P = .047$). Sitagliptin was administered to 3 patients who were subsequently treated with other DPP-4 inhibitors.

The Association Between DPP-4 Inhibitor Intake and the Development of BP

A statistically significant association was observed between DPP-4 inhibitor intake and the development of BP (OR, 2.83;

95% CI, 1.70-4.71). The strongest association was observed in patients younger than 70 years (OR, 5.59; 95% CI, 1.73-18.01) followed by patients aged 70 to 79 years (OR, 3.20; 95% CI, 1.11-9.25), and patients older than 80 years (OR, 2.40; 95% CI, 1.18-4.91). The association was stronger among male (OR, 4.46; 95% CI, 2.11-9.40) than female (OR, 1.88; 95%, CI 0.92-3.86) patients (**Table 2**).

Use of vildagliptin demonstrated the strongest association with BP (OR, 9.28; 95% CI, 4.54-18.99). Although statistically significant in both sexes, the association was stronger in males (OR, 21.38; 95% CI, 7.12-64.21) than in females (OR, 4.12; 95% CI, 1.49-11.42; **Table 3**).

Use of linagliptin was significantly associated with the development of BP (OR, 6.61; 95% CI, 2.28-19.17). This association was significant both among male (OR, 5.84; 95% CI, 1.25-27.33) and female (OR, 7.39; 95% CI, 1.70-32.25) patients (Table 3).

No significant association was revealed between the administration of sitagliptin and the development of BP. Although less frequent among case patients, the use of sitagliptin did not have a statistically significant protective effect (OR, 0.42; 95% CI, 0.17-1.01). In sex-specific analysis, the association lacked any statistical significance (OR, 0.42; 95% CI, 0.12-1.45 in males; OR, 0.42; 95% CI, 0.12-1.47 in females; Table 3).

A "leave-one-out" sensitivity analysis was conducted. The adjusted ORs following the exclusion of vildagliptin-, linagliptin-, and sitagliptin-related cases were 1.18 (95% CI, 0.59-2.36), 2.32 (95% CI, 1.34-4.01), and 8.82 (95% CI, 5.58-16.98), respectively.

Multivariate Analysis

After controlling for confounding factors implicated with an increased risk for BP such as comorbid neurological conditions[21] as well as for metformin administration, DPP-4 inhibitor intake seemed to be independently associated with the development of BP in multivariate logistic regression analysis (adjusted OR, 3.16; 95% CI, 1.86-5.37). The adjusted ORs for vildagliptin and linagliptin were 10.67 (95% CI, 5.09-22.36) and 6.65 (95% CI, 2.24-19.72), respectively (Table 3).

Analysis of the Independent Role of Metformin

Of the 36 patients treated with DPP-4 inhibitor, 16 (44%) underwent treatment with combined agents containing vildagliptin/sitagliptin with metformin (Eucreas; Novartis and Januet; Merck). Overall, 51 case patients (62%) and 218 controls (66.5%) were prescribed metformin, whether alone or in combination with DPP-4 inhibitor (P = .46). Metformin

Table 1. Demographic Features of Study Participants

Characteristic	Patients With BP (n = 82)	Controls (n = 328)	*P* Value
Age, mean (SD), y	79.1 (9.1)	79.0 (9.0)	.93
Median (range)	81.0 (56.0-95.0)	81.0 (50.0-99.4)	
Female sex, No. (%)	44 (53.7)	176 (53.7)	>.99
Ethnicity, No (%)			>.99
Jewish	67 (81.7)	268 (81.7)	
Arab	15 (18.3)	60 (18.3)	

Abbreviation: BP, bullous pemphigoid.

Table 2. Univariate Analysis of the Risk for BP Under DPP-4 Inhibitor Exposure, Stratified by Sex and Age

Subgroup	No.	DPP-4 Inhibitor Exposure, No. (%)		OR (95% CI)	*P* Value
		Patients With BP (n = 82)	Controls (n = 328)		
All	410	36 (43.9)	71 (21.6)	2.83 (1.70-4.71)	<.001
Age, y					
0-69	71	10 (58.8)	11 (20.4)	5.58 (1.73-18.01)	.002
70-79	111	10 (58.8)	29 (30.9)	3.20 (1.11-9.25)	.03
≥80	228	16 (33.3)	31 (17.2)	2.40 (1.18-4.91)	.01
Sex					
Male	190	21 (55.3)	33 (21.7)	4.46 (2.11-9.40)	<.001
Female	220	15 (34.1)	38 (21.6)	1.88 (0.92-3.86)	.08

Abbreviations: BP, bullous pemphigoid; DPP-4 inhibitor, dipeptidyl peptidase 4 inhibitor; OR odds ratio.

Table 3. Univariate and Multivariate Analyses of the Risk for BP by Each DPP-4 Inhibitor Agent and Metformin

DPP-4 Exposure Agent	No. (%)		OR (95% CI)	Univariate *P* Value	OR (95% CI)			Multivariate *P* Value
	BP (n = 82)	Controls (n = 328)			Male-Specific	Female-Specific	Adjusted[a]	
Overall	36 (43.9)	71 (21.6)	2.83 (1.70-4.71	<.001	4.46 (2.11-9.40)	1.88 (0.92-3.86)	3.16 (1.86-5.37)	<.001
Vildagliptin	24 (29.3)	14 (4.3)	9.28 (4.53-18.99)	<.001	21.38 (7.12-64.21)	4.12 (1.49-11.42)	10.67 (5.09-22.36)	<.001
Linagliptin	9 (11.0)	6 (1.8)	6.62 (2.28-19.17)	<.001	5.84 (1.25-27.33)	7.39 (1.70-32.25)	6.65 (2.24-19.72)	<.001
Sitagliptin	6[b] (7.3)	51 (15.5)	0.42 (0.17-1.01)	.047	0.42 (0.12-1.45)	0.42 (0.12-1.47)	0.43 (0.18-1.05)	.07
Metformin	51 (62.2)	218 (66.5)	0.83 (0.50-1.37)	.47	1.06 (0.51-2.21)	0.67 (0.34-1.33)	0.83 (0.51-1.38)	.47

Abbreviations: BP, bullous pemphigoid; DPP-4 inhibitor, dipeptidyl peptidase 4 inhibitors; OR odds ratio.

[a] Adjusted for neurological diseases and metformin intake.

[b] Three of these patients were treated with 2 agents.

Table 4. Characteristics of Patients With DPP-4 Inhibitor–Associated BP and Those With Non–DPP-4 Inhibitor–Associated BP[a]

Characteristic	DPP-4 Inhibitor–Associated BP (n = 36)	Non–DPP-4 Inhibitor–Associated BP (n = 46)	*P* Value
Age at diagnosis, y			.28
Mean (SD)	77.9 (9.8)	80.1 (8.3)	
Median (range)	77.5 (59.0-94.0)	82.0 (56.0-95.0)	
Sex			.056
Male	21 (58.3)	17 (37.0)	
Female	15 (41.7)	29 (63.0)	
Delay at diagnosis, mean (SD), mo	3.4 (3.2)	2.6 (2.7)	.22
Atypical clinical variants of BP[b]	5 (13.9)	4 (8.7)	.46
Distribution of bullous lesions			
Mucosal involvement	8 (22.2)	3 (6.5)	.04
Limbs	35 (97.1)	46 (100)	.25
Trunk	35 (97.1)	41 (88.9)	.16
Hands and/or feet	12 (33.3)	17 (36.9)	.74
Head and neck	16 (44.4)	17 (37.8)	.55
Severity			.28
Extensive disease	20 (55.6)	20 (43.5)	
Mild to moderate	16 (44.4)	26 (56.5)	
Anti-basement membrane antibodies detected by indirect IF	14 (38.9)	26 (56.5)	.12
Treatment			
Oral prednisone >1 mg/kg	22 (61.3)	30 (65.0)	.73
Prednisone dose at discharge, mean (SD), mg	39.4 (18.8)	42.6 (17.3)	.43
Adjuvant immunosuppressant	15 (41.7)	11 (23.9)	.09
Topical steroids	4 (11.1)	4 (8.7)	.72
Peripheral eosinophilia			
Eosinophil count, mean (SD), cells/μL	399.8 (508.0)	1117.6 (1847.6)	.01
Other hematologic biomarkers, mean (SD)			
WBC count, cells/μL	9163.0 (3082.6)	10 052.2 (3593.3)	.24
Platelet count, $\times 10^3$/μL	226.5 (67.5)	264.4 (75.8)	.02
ESR, mm/h	35.4 (28.1)	34.1 (19.4)	.81

Abbreviations: BP, bullous pemphigoid; DPP-4 inhibitor, dipeptidyl peptidase 4 inhibitor; ESR, erythrocyte sedimentation rate; IF, immunofluorescence; WBC, white blood cell.

[a] Unless otherwise indicated, data are reported as number (percentage) of participants.

[b] Including the prurigo-like type, urticaria-like type, eczema-like type, and dyshidrosiform type.

administration was not associated with an increased risk for BP, neither in univariate analysis (OR, 0.83; 95% CI, 0.50-1.37), nor in multivariate analysis adjusting for neurological conditions (adjusted OR, 0.83; 95% CI, 0.51-1.38) (Table 3).

Comparison Between Patients With DPP-4 Inhibitor-Associated BP and Non-DPP-4 inhibitor-Associated BP

We then addressed the differences between case patients undergoing treatment with DPP-4 inhibitor (n = 36) compared with case patients without DPP-4 inhibitor exposure (n = 46). The demographic composition of the 2 subgroups was similar, excluding the slightly higher proportion of males in the DPP-4 inhibitor–associated subgroup (n = 21; 58% vs n = 17; 37%; *P* = .06). Regarding the anatomical distribution of bullous lesions, patients with DPP-4 inhibitor exposure had a greater rate of involvement of mucosal surfaces (22.2% vs 6.5%; *P* = .04). Involvement of other body sites, severity, and the proportion of atypical clinical variants of BP (including the prurigo-like type,[22] urticaria-like type,[23] eczema-like type,[24] and dyshidrosiform type[25]) were similar between the 2 subgroups (**Table 4**).

Patients with BP who were not exposed to DPP-4 inhibitor had significantly higher mean (SD) circulating eosinophil counts (1117.6 [1847.6] vs 399.8 [508.0] cells/μL; *P* = .01) and greater prevalence of peripheral eosinophilia (55.6% vs 22.2%; *P* = .002). Other hematologic biomarkers did not differ substantially between the 2 subgroups except for platelet count being higher among patients with BP who were not exposed to DPP-4 inhibitor (264.4 [75.8] × 10^3/μL vs 226.5 [67.5] × 10^3/μL; *P* = .02) (Table 4).

Clinical Course Following Discontinuation of DPP-4 Inhibitor Treatment

The median latency between the initiation of DPP-4 inhibitor use and the onset of BP was 10.4 months (range, 1.0-26.5 months). All patients in our cohort, whether the drug treatment was stopped or not, were treated in accordance with our center's protocol. Of the 36 patients who developed BP after DPP-4 inhibitor exposure, the treatment had been stopped in 19 (53%). Of those 19 patients, 6 (32%) experienced complete remission off therapy, and 9 (47%) experienced complete remission on minimal therapy. Three

patients (16%) achieved only partial remission on therapy (1 of these died due to septicemia 12 months after BP diagnosis). One patient had recurrent relapses, ending in death due to pneumonia 18 months following diagnosis of BP.

The clinical outcomes were less favorable among the 13 patients (36%) for whom DPP-4 inhibitor treatment was not discontinued. Eight deaths occurred between 2 months and 4.9 years from the initial diagnosis in this subgroup. Only 3 (23%) patients achieved complete remission off therapy, and 4 (31%) achieved complete remission on minimal therapy. The status of DPP-4 inhibitor intake after diagnosis was not available for 4 patients (11.1%).

It should be stated that patients who discontinued DPP-4 inhibitor treatment were slightly younger than patients with persistent exposure (mean [SD] age, 75.2 [9.7] vs 80.8 [7.8] years; $P = .08$). The median time of follow-up was 2.01 years (range, 0.1-7.0 years), with the contribution of 88.8 person-years.

Discussion

This case-control study emphasizes that DPP-4 inhibitor exposure is associated with an increased risk for BP (adjusted OR, 3.16) . Of note is the substantial role of vildagliptin and, to a lesser extent, linagliptin, which were shown to increase the likelihood of disease development by adjusted ORs of 10.67 and 6.65, respectively. The association was independent of metformin exposure and was stronger both among males and patients younger than 70 years. Patients with DPP-4 inhibitor–associated BP presented with a higher rate of mucosal involvement and lower peripheral eosinophil counts. Discontinuation of DPP-4 inhibitor treatment appeared to induce better clinical outcomes.

The association Between DPP-4 inhibitor and BP has been investigated in 2 other controlled studies. Benzaquen et al[16] found that DPP-4 inhibitor exposure was associated with an increased risk for developing BP (adjusted OR, 2.64), with vildagliptin being implicated with the highest risk (adjusted OR, 3.57). Given the relatively small sample size (n = 61) and the low control-to-case ratio (2:1), this study was underpowered to validate or refute the association with less frequently used DPP-4 inhibitor medications, such as linagliptin and sitagliptin. In addition, this study did not analyze the isolated role of metformin, which is of great importance because DPP-4 inhibitor agents are often given in combination with metformin (44.4% in our cohort). Owing to a larger sample size and a greater recruitment of control participants, we were able to demonstrate that linagliptin was associated with a 6.6-fold increased risk for BP. Furthermore, we were able to prove that the association between BP and DPP-4 inhibitor exists regardless of metformin exposure.

The second study, performed recently by Varpuluoma et al,[17] found that DPP-4 inhibitor exposure was associated with 2.2-fold increased risk for BP, particularly with vildagliptin (adjusted OR, 10.4). This study did not analyze the association between BP and linagliptin, most likely owing to the limited number of cases treated with this agent. This study also did not exclude patients with diabetes (in both case and control groups), which may lead to a differential bias, as patients with BP are much more susceptible to developing diabetes than their age- and sex-matched counterparts, and have, therefore, a higher probability of receiving treatment with antidiabetic drugs including DPP-4 inhibitors.

Characteristics of Study Patients With DPP4-Associated BP

The clinical and immunological characteristics of DPP-4 inhibitor–associated BP have been elucidated in 2 Japanese studies. Izumi et al[26] reported that 7 patients with DPP-4 inhibitor–associated BP tended to present with the noninflammatory phenotype, characterized by reduced erythema and scant lesional eosinophilic infiltration. These patients demonstrated autoantibody reactivity against the midportion of BP-180, but not against the immunodominant NC-16A domain of BP-180. Recently, Chijiwa et al[27] reported that the number of eosinophils infiltrating into the skin, but not circulating eosinophils, was significantly lower in 9 patients with DPP-4 inhibitor–related BP than in 21 patients with non–DPP-4 inhibitor–related BP. In addition, these patients had more frequent mucosal involvement. The findings of the present study, which included 2.5-fold and 4-fold more patients than the earlier studies Izumi et al[26] and Chijiwa et al,[27] respectively, support the higher mucosal involvement but contrast with the peripheral eosinophilia findings. The present study also found a similar age of presentation in all patients with BP, with or without association with DPP-4 inhibitor, concurring with the findings of Chijiwa et al[27] and Varpuluoma et al.[17]

The median latency between the initiation of treatment with DPP-4 inhibitor medication and the onset of BP varies substantially among different reports, ranging from 6.0 to 26.4 months.[14,16,17,27] The median latency in our cohort (10.4 months) was within the middle range of these previous studies. Therefore, DPP-4 inhibitor may be suspected as a provocative factor for BP even if it had been administered for over 2 years prior to the onset of BP.

The favorable clinical outcomes following the discontinuation of treatment with the associated agents are in line with the findings of Benzaquen et al,[16] who reported that 95% of patients experienced complete or partial remission under standard treatment after discontinuation of DPP-4 inhibitor treatment. Similarly, the EudraVigilance database reveals that 60.2% of sitagliptin-, 66.9% of vildagliptin-, and 51.2% of linagliptin-associated BP patients had recovered or were recovering at the time of the report (http://www.adrreports.eu). It is noteworthy that all patients, regardless of DPP-4 inhibitor treatment discontinuation, were treated according to the standard treatment protocol of our center. However, in patients for whom DPP-4 inhibitor treatment was discontinued, a better clinical course was observed than among patients with persistent DPP-4 inhibitor exposure. The accumulation of accordant results from 3 unrelated sources should prompt the discontinuation of treatment with DPP-4 inhibitor medications when the diagnosis of BP is made. Since metformin was not independently associated with BP, a diagnosis of BP during metformin/DPP-4 inhibitor combination therapy allows for metformin to be safely continued.

Interpretation and Implication of Findings

The pathomechanism underlying the association between DPP-4 inhibitor and BP has yet to be elucidated. However, it is known that DPP-4 is a cell-surface plasminogen receptor that activates plasminogen, leading to the formation of plasmin,[28] which is a major serine protease that cleaves BP-180 within the immunodominant NC-16A domain and can be detected in lesional skin as well as in blister fluid in BP.[29] The inhibition of plasmin by DPP-4 inhibitor may lead to alterations in the appropriate cleavage of BP-180, which may affect its antigenicity and function.[26] It is well established that keratinocytes and other cell types, such as endothelial and T cells, express DPP-4, inhibition of which may increase the activity of eotaxin and other proinflammatory cytokines, leading to cutaneous eosinophil activation and blister formation.[30]

The considerable prevalence of DPP-4 inhibitor exposure among patients with BP in our cohort (43.9%) and the increased risk associated with these agents for triggering BP, may in part account for the 1.9-fold increasing incidence of BP recently observed in our region; from 7.6 cases per million per year in the 2000-2005 period to 14.3 cases per million per year in the 2011-2015 period ($P < .001$).[5]

Limitations and Strengths

The main limitation of the present study arises from the retrospective data collection. Given that the study was carried out in a tertiary referral center setting, it is susceptible to the selection of more severe and recalcitrant cases. The wide 95% CIs in some of the subgroup analyses may reflect the existence of sparse-data bias occurring when stratification creates sparse cell sizes.[31] The small number of DPP-4–inhibitor exposed patients among both cases and controls for linagliptin and in cases for sitagliptin may interfere with drawing firm conclusions. Further large-scale studies are warranted to fill this gap. In addition, the generalizability of our findings may be hampered by the single-center setting and the sample and subsample imbalances. Propensity score matching could not be performed due to database limitations; this could have enhanced the precision of the estimates of the study. Nonetheless, our study comprises the largest clinically and immunologically characterized subgroup of patients with BP who were exposed to DPP-4 inhibitor and is current enough to assess the risk for BP associated with linagliptin use for the first time.

In conclusion, use of DPP-4 inhibitor overall and vildagliptin and linagliptin individually was found to increase the risk for BP significantly. Patients with DPP-4 inhibitor–associated BP presented more frequently with lesions on the mucosal surfaces and had lower peripheral eosinophilia. Discontinuation of treatment with DPP-4 inhibitors was followed by better clinical outcomes, suggesting that such discontinuation should be considered when the diagnosis of BP is established. The increased exposure to these agents in recent years may account for the increasing incidence of BP in our region.

ARTICLE INFORMATION

Accepted for Publication: May 23, 2018.

Published Online: August 8, 2018. doi:10.1001/jamadermatol.2018.2352

Author Contributions: Dr Kridin had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.
Concept and design: Kridin.
Acquisition, analysis, or interpretation of data: Kridin, Bergman.
Drafting of the manuscript: Kridin.
Critical revision of the manuscript for important intellectual content: Kridin, Bergman.
Statistical analysis: Kridin.
Administrative, technical, or material support: Kridin, Bergman.
Study supervision: Bergman.

Conflict of Interest Disclosures: None reported.

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