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Dipeptidyl peptidase-IV inhibitors, a risk factor for bullous pemphigoid. Retrospective multicenter case-control study in France and Switzerland

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1 **Original article**

2 **Dipeptidyl peptidase-IV inhibitors, a risk factor for bullous pemphigoid. Retrospective**
3 **multicenter case-control study in France and Switzerland**

4

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21

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43 **Capsule summary**

44 What is already known on this topic: Case reports suggest an association between dipeptidyl
45 peptidase-IV inhibitors and development of bullous pemphigoid.

46 What this article adds to our knowledge: This case-control study confirms an increased risk of
47 developing bullous pemphigoid in patients receiving dipeptidyl peptidase-IV inhibitors.

48 How this information impacts clinical practice and/or changes patient care: Dipeptidyl
49 peptidase-IV inhibitors, especially vildagliptin, should be used cautiously in high-risk diabetic
50 patients, ie. males and older than 80 years.

51 **Abstract**

52 **Background:** Case reports have suggested an association between dipeptidyl peptidase-IV
53 inhibitors (DPP4i) and development of bullous pemphigoid (BP).

54 **Objective:** To evaluate the association between DPP4i treatment and development of BP.

55 **Methods:** We conducted a retrospective 1:2 case-control study, comparing diabetic BP cases
56 to age and sex-matched diabetic controls, issued from Swiss (Bern) and French (Marseille)
57 dermatological departments, from January 1st 2014 to July 31st 2016.

58 **Results:** We collected 61 diabetic BP patients and 122 controls. DPP4i were associated with
59 an increased risk of developing BP (adjusted OR=2.64; 95% CI: 1.19-5.85; p=0.02), with
60 vildagliptin showing the highest adjusted OR (3.57; 95% CI: 1.07-11.84; p=0.04). Stratified
61 analysis showed a stronger association in males and patients aged 80 years or older. DPP4i
62 withdrawal and the institution of first-line treatments led to clinical remission in 95% of
63 cases.

64 **Limitations:** This was a retrospective study in tertiary referral hospitals. We focused the
65 analysis on DPP4i intake, without analyzing the potential isolated effect of metformin.

66 **Conclusions:** DPP4i, especially vildagliptin, are associated with an increased risk of
67 developing BP. Their use needs to be carefully evaluated, particularly in high-risk patients,
68 such as males and those aged 80 years or older.

69 **Introduction**

70 Bullous pemphigoid (BP) is the most frequent autoimmune subepidermal blistering disease
71 which typically affects the elderly. Its cutaneous manifestations are polymorphic, ranging
72 from pruritus with excoriated, eczematous, papular and/or urticaria-like lesions in the non-
73 bullous phase, to vesicles and bullae in the bullous phase (1). BP is associated with an
74 immune response directed against two molecules, the BP antigen 180 (BP180, BPAG2), and
75 the BP antigen 230 (BP230, BPAG1) (2).

76 Since the publication of the first case of BP associated with sulfasalazine in 1970, a wide
77 range of drugs (spironolactone, furosemide, chloroquine, beta-blockers and several
78 antibiotics) have been associated with the disease (3). Recently, several cases of BP have been
79 reported in association with dipeptidyl peptidase-IV inhibitors (DPP4i), also known as
80 gliptins (7-16).

81 DPP4i are oral anti-hyperglycemic drugs administered to patients with type 2 diabetes in
82 monotherapy or in combination with other oral anti-hyperglycemic medications or insulin.
83 DPP4 is an enzyme that inactivates incretins (glucagon-like peptide-1 and glucose-dependent
84 insulinotropic polypeptide). DPP4i increase levels of incretins, thereby increasing insulin
85 secretion, decreasing glucagon secretion and improving glycemic control. Sitagliptin was first
86 approved in 2006 by the U.S. Food and Drug Administration, followed by saxagliptin (2009),
87 linagliptin (2011) and alogliptin (2013). Three DPP4i are currently available on the French
88 market and five DPP4i on the Swiss market: sitagliptin and vildagliptin (2007), saxagliptin
89 (2009) and, only on Swiss market, linagliptin (2011) and alogliptin (2013). They are used
90 alone or in association with metformin in the same tablet (7).

91 An increasing number of clinical reports and pharmacovigilance database analyses have been
92 published, suggesting an association between DPP4i intake and BP. Nevertheless, this has not
93 been confirmed by a well-designed controlled study.

94 The main objective of our case-control study was, therefore, to retrospectively evaluate the
95 association between DPP4i treatment and development of BP. The secondary endpoints were
96 to determine a potential higher association for a specific DPP4i, and to evaluate the disease
97 course after DPP4i withdrawal.

98 **Materials and methods**

99 The investigations were conducted as a retrospective case-control study with 1:2 design,
100 comparing BP diabetic cases to age and sex-matched type 2 diabetic controls, from January
101 1st 2014 to July 31st 2016. All study procedures adhered to the Declaration of Helsinki
102 Principles. The French committee for the protection of persons (RO-2016/37) and the ethics
103 committee of the Canton of Bern (KEK-2016/01488) approved the study. The French
104 advisory committee on information processing in material research in the field of health
105 (CCTIRS) and the French commission for information technology and civil liberties (CNIL)
106 also authorized this study.

107

108 ***Data collection for cases and controls***

109 The study was conducted in three University dermatological departments (Bern, Marseille
110 Nord, and Marseille La Timone). By using the database of the respective histopathology
111 departments and clinical records, we identified all patients with BP diagnosed for the first
112 time between January 1st 2014 and July 31st 2016. The diagnosis of BP was based on the
113 following criteria, developed by the French bullous study group (4): consistent clinical
114 features, compatible histopathology findings, positive direct immunofluorescence (DIF)
115 studies and in some cases, positive indirect immunofluorescence microscopy (IIF) studies
116 and/or positive ELISA-BP180/ELISA-BP230 (MBL International, Japan). Among these BP
117 patients, we identified the cases having type 2 diabetes.

118

119 For these patients, we recorded: age, sex, date of BP diagnosis, treatment of BP (topical
120 steroids, systemic corticosteroids, immune suppressors, other treatments such as doxycycline
121 or dapsone), evolution of BP (complete remission, partial remission, relapse, death),
122 comorbidities (rheumatic, neurological, cardio-vascular, digestive diseases, neoplasia, etc.),
123 treatment with DPP4i, and other co-treatments (diuretics, antibiotics, neuroleptics, NSAID,
124 antihypertensive drugs, etc.).

125 If a DPP4i was mentioned in the medical record, we examined the type of DPP4i, the
126 chronology between BP diagnosis and onset of the DPP4i treatment, and the evolution after
127 DPP4i withdrawal. Patients suffering from other autoimmune bullous diseases, or who did not
128 otherwise fulfill the inclusion criteria, were not included.

129

130 The controls were obtained between January 1st 2014 and July 31st 2016 from the
131 endocrinology departments of the same hospitals. For each case, two diabetic control patients,
132 visiting the endocrinology department in the same 6-month period and matched to the case by
133 gender and quinquennium of age, were then randomly selected from all available patients
134 satisfying the matching criteria. The patient files were reviewed concerning treatment for
135 diabetes, specifically the use of DPP4i, other co-treatments and comorbidities. For the
136 controls, we did not include patients suffering at the time of the study from any chronic skin
137 diseases, including bullous dermatosis.

138 We then compared exposure to DPP4i between cases and controls with adjustment for
139 potential confounders.

140

141 *Statistical analysis*

142 Descriptive data were presented as number with percentages or means with standard
143 deviations (SD) for categorical and continuous variables respectively. Mann-Whitney U test
144 was used to assess possible residual differences in the distribution of age between cases and
145 controls. Differences between cases and matched controls across different levels of other
146 factors were assessed by means of univariate conditional logistic regression analysis. Factors
147 associated to DPP4i use were also investigated by means of Pearson's χ^2 test or Fisher's exact
148 test, where required.

149 All factors with p-value <0.10 in the univariate case-control analysis and associated to DPP4i
150 use, with p-value <0.10 at univariate level, were evaluated as possible confounding factors in
151 multivariate conditional logistic regression models with backward stepwise selection
152 algorithm. Factors retained for adjustment were: neurological and metabolic/endocrine
153 comorbidities, as well as other dermatological conditions unrelated with BP. The effect of
154 DPP4i use on BP onset in diabetic patients was expressed in terms of odds ratio (OR) along
155 with its 95% confidence interval (CI) and p-value. A stratified analysis by possible effect
156 modifiers, including gender and age group, was also performed. All tests were considered
157 statistically significant at p-value <0.05.

158 Before starting the study, we planned to recruit at least 183 patients (61 cases and 122
159 controls) in order to detect OR >2.5 in a 1:2 matched case-control design, supposing to
160 observe a 30% exposure to DPP4i use in the control group, ($\alpha=0.05$, $\beta=0.20$, multiple
161 correlation coefficients <0.2). Analyses were carried out by using SPSS software v. 20.0
162 (Armonk, NY: IBM Corp.).

163 **Results**

164 From January 2014 to July 2016, 165 patients were diagnosed with BP (61 in Bern, 47 in
165 Marseille Nord and 57 in Marseille La Timone). Among these, 61 were diabetic (22 in Bern,
166 14 in Marseille Nord and 25 in Marseille La Timone). We collected two matched controls for
167 each case, resulting in a total of 122 controls.

168 50.8% of cases were females and the mean age was 79.1 ± 7.0 years. The main comorbidities
169 of cases were cardio-vascular (86.9%), neurological (52.5%), metabolic and endocrine, other
170 than diabetes (39.3%) and uronephrological diseases (39.3%) (Table 1).

171 In our three investigational centers, we collected 28 diabetic patients with BP on DPP4i.
172 DPP4i were used more frequently in BP cases (45.9%) than in controls (18%) and the
173 difference was statistically significant ($p < 0.001$). Of the specific DPP4i, vildagliptin was
174 more common in cases (23%) compared to controls (4.1%). For the other co-treatments, there
175 was no statistical difference between cases and controls, except for the use of antihistamines
176 ($p < 0.001$). There were no differences in other anti-diabetic medications, including
177 metformin, between cases and controls ($p = 0.08$) (Table 2).

178 All cases of BP received high potency topical steroids as first line treatment. Systemic
179 corticosteroids were used in half of cases (50.8%), immunosuppressive agents in 32.8% of
180 cases, and other treatments such as doxycycline or dapsone in 34.4% of cases. With treatment,
181 37.7% went into complete remission and 42.6% went into partial remission. Finally, there
182 were no differences in treatment between the DPP4i diabetic BP and the non-DPP4i diabetic
183 BP (data not shown), an observation suggesting that presentation and initial severity of BP in
184 these two groups were similar.

185 ***DPP4i and BP***

186 The univariate analysis of the association between DPP4i use and BP in diabetic patients
187 found an OR of 3.45 (95% CI: 1.76-6.77; $p < 0.001$). After adjustment for possible
188 confounding factors associated to BP onset and DPP4i use in multivariate analysis, the OR
189 was 2.64 (95% CI: 1.19-5.85; $p = 0.02$) (Table 3).

190 A more detailed analysis of DPP4i use found a higher association for vildagliptin, with a
191 crude OR of 7.23 (95% CI: 2.44-21.40; $p = 0.001$) and an adjusted OR of 3.57 (95% CI: 1.07-
192 11.84; $p = 0.04$). The study was underpowered to detect differences between other DPP4i,
193 linagliptin and alogliptin being only used in the Swiss cases.

194 Gender-stratified analysis indicated that the effect of DPP4i on BP onset was higher in males
195 (adjusted OR = 4.36; 95% CI: 1.38-13.83; p = 0.01) than females (adjusted OR = 1.64; 95%
196 CI: 0.53-5.11; p = 0.39). Age group-stratified analyses showed a stronger association for
197 patients aged 80 years or older, with an adjusted OR of 5.31 (95% CI: 1.60-17.62; p = 0.006).

198 *Clinical course of BP patients under DPP4i*

199 In our three centers, we collected in total 28 diabetic patients developing BP under DPP4i
200 exposure. The duration of DPP4i use and onset of BP ranged from 10 days until 3 years
201 (median = 8.2 months).

202 Drug withdrawal was performed in 19 patients on suspected DPP4i-associated BP. Complete
203 (11/19; 58%) or partial (7/19; 37%) remission with some mild persistent disease was obtained
204 for all patients but one (duration of follow up 3-30 months, median= 16.4 months). First-line
205 treatment was high potency topical steroids and systemic corticosteroids in severe or
206 refractory cases followed by a standard tapering schedule (5, 6). No further therapy was
207 necessary in these patients after DPP4i withdrawal to obtain BP remission. For one patient,
208 sitagliptin was initially stopped, leading to a partial remission, but its reintroduction combined
209 with metformin led to a relapse of the BP. Definitive discontinuation of sitagliptin and its
210 replacement by repaglinide resulted in a partial remission of BP with 12-month follow-up.
211 The clinical outcome in the nine patients, in which DPP4i were not stopped, was unfavorable.
212 There were three deaths of unknown causes (33%), one relapse (11%), four partial remissions
213 (45%), and one complete remission (11%).

214

215 **Discussion**

216 Our study demonstrates that DPP4i are associated with an increased risk of developing BP,
217 with an adjusted OR of 2.64. Association with vildagliptin was significantly higher compared
218 to that with other DPP4i with an adjusted OR of 3.57. Our findings further indicate that the
219 rate of DPP4i intake in patients with BP is higher both in male patients and in patients older
220 than 80 years. Finally, DPP4i withdrawal seems to have a favorable impact on the outcome of
221 BP diabetic patients, as 95% of them went into remission after management with first-line
222 therapeutic options (ie, topical and sometimes systemic corticosteroids).

223 An increasing number of reports have suggested that DPP4i trigger BP. Fourteen (74%) out of
224 the 19 described BP cases appeared to be related to vildagliptin intake. The median age of
225 affected patients was 72.5 years with an almost identical number of males and females (8-16).
226 In our study, among the 28 diabetic patients developing BP under DPP4i exposure, males
227 were more affected (56.7%) and the median age was 80 years.

228 Garcia *et al.* (8) identified 170 cases of BP in patients on DPP4i in the EudraVigilance
229 database, suggesting that the intake of DPP4i was more frequently associated with the
230 development of BP when compared to that of other drugs. In the latter, a disproportionately
231 high number cases using vildagliptin were found. A French case-non-case study recording all
232 spontaneous reports of DPP4i-related BP in the National Pharmacovigilance Database
233 between 04/2008 and 08/2014 also provided evidence for an increased risk of BP associated
234 to DPP4i exposure, especially vildagliptin (7). Our present study confirms that the association
235 with vildagliptin is stronger than that for the other DPP4i. This cannot be explained by an
236 overprescription of vildagliptin compared to that of other DPP4i. In our control group,
237 sitagliptin was the most prescribed DPP4i with 14 diabetic patients (11.5%), whereas only 5
238 patients were treated by vildagliptin (4%). Increased prescribing of sitagliptin was confirmed
239 by an analysis of drug sales in France published by the ANSM (French National Agency for
240 Medicines and Health Products Safety) in 2014. In this survey, sitagliptin was the most
241 prescribed DPP4i and the 24th highest earning drug in 2013, whereas vildagliptin was not
242 ranked. A recent retrospective study suggests that DPP4i-associated BP is frequently non- or
243 pauci- inflammatory characterized by small blisters, mild erythema, and a limited skin
244 distribution. The latter is potentially related to a distinct reactivity profile of autoantibodies to
245 BP180 (17). Although in our retrospective evaluation, there was no apparent difference in

246 clinical presentation and initial management between DPP4i diabetic BP patients and non-
247 DPP4i diabetic BP patients (data not shown), prospective studies are required to address the
248 question whether BP associated with the intake of DPP4i has unique clinical and
249 immunological features.

250 The pathophysiological mechanisms linking DPP4i intake and BP development remain
251 unclear. DPP4i could induce BP *de novo* or accelerate the development of BP in susceptible
252 individuals. Many cell types, including keratinocytes, T-cells and endothelial cells,
253 constitutionally express DPP4. DPP4 inhibition could enhance the activity of
254 proinflammatory chemokines, like eotaxin, promoting eosinophil activation in the skin, tissue
255 damage and blister formation (18). Thielitz *et al.* reported that DPP4i have an antifibrogenic
256 activity by decreasing TGF- β_1 expression and secretion of procollagen type I (19). All these
257 effects could be higher for vildagliptin than other DPP4i due to molecular differences.
258 Furthermore, vildagliptin administration in monkeys resulted in dose-dependent and
259 reversible skin effects, such as blister formation, peeling, and erosions (20).

260 Finally and more importantly, DPP4 is a cell surface plasminogen receptor that is able to
261 activate plasminogen leading to plasmin formation. Plasmin is a major serine protease that is
262 known to cleave BP180 within the juxtamembranous extracellular noncollagenous 16A
263 domain. Hence, the inhibition of plasmin by DPP4i may change the proper cleavage of
264 BP180, affecting by this means its antigenicity and its function (17).

265 Our study has some limitations: we focused the analysis on DPP4i intake, while the potential
266 isolated effect of metformin was not analyzed. Nevertheless, after DPP4i withdrawal,
267 metformin was either continued (in those cases in which it was initially combined with
268 DPP4i) or newly started in 8 of our BP patients. Among the latter, we observed 5 complete
269 and three partial remissions on follow-up. In addition, metformin intake has not been
270 implicated so far in the development of BP. Based on these observations, it is unlikely that
271 metformin plays a triggering role but specific studies should be designed to examine the effect
272 of metformin on its own. Finally, we included BP patients identified by searching our
273 histopathology databases. It is therefore possible that we missed a number of BP cases in
274 which either the term “pemphigoid” was not used in the corresponding histopathological
275 report or BP was not clinically and/or histopathologically considered.

276 In conclusion, our findings in a case-control study confirm that DPP4i are associated with an

277 increased risk of developing BP in diabetic patients. Therefore, the prescription of DPP4i,
278 especially vildagliptin, should potentially be limited or avoided in high-risk patients,
279 including males and those aged 80 years or older. A larger prospective study might be useful
280 to confirm our findings.

281 **Abbreviations:**

282 BP, Bullous pemphigoid

283 DPP4i, Dipeptidyl peptidase-IV inhibitors

284 OR, Odds ratio

285 CI, Confidence interval

286 SD, Standard deviation

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362 **Table 1** - Demographics and comorbidities of selected cases and controls

363

		Controls		Cases		Total		p*
		N	%	N	%	N	%	
Gender	Male	60	49.2%	30	49.2%	90	49.2%	-
	Female	62	50.8%	31	50.8%	93	50.8%	
Age, yrs (<i>mean, SD</i>)		79.3	7.0	78.7	7.2	79.1	7.0	0.63
< 75		30	24.6%	17	27.9%	47	25.7%	
75 - 84		62	50.8%	29	47.5%	91	49.7%	
85+		30	24.6%	15	24.6%	45	24.6%	
Comorbidities	Neurological	47	38.5%	32	52.5%	79	43.2%	0.06
	Cardiovascular	108	88.5%	53	86.9%	161	88.0%	0.75
	Rheumatic	36	29.5%	11	18.0%	47	25.7%	0.10
	Digestive	34	27.9%	19	31.1%	53	29.0%	0.65
	Metabolic and endocrine**	85	69.7%	24	39.3%	109	59.6%	<0.001
	Pulmonary	27	22.1%	17	27.9%	44	24.0%	0.41
	Uronephrological	45	36.9%	24	39.3%	69	37.7%	0.74
	Neoplasia	29	23.8%	12	19.7%	41	22.4%	0.49
	Dermatological***	5	4.1%	12	19.7%	17	9.3%	0.03
	Other	35	28.7%	23	37.7%	58	31.7%	0.18

364 SD: standard deviation, yrs: years

365 * Mann-Whitney U test was used to assess possible residual differences in the distribution of
366 age between cases and age and gender matched controls. Differences between cases and
367 matched controls across different levels of other factors were assessed by means of univariate
368 conditional logistic regression analysis.

369 ** except for diabetes

370 *** except for BP

371 **Table 2-** DPP4i use and other co-treatments in selected cases and controls

372

		Controls		Cases		Total		P*
		N	%	N	%	N	%	
DPP4i	None	100	82.0%	33	54.1%	133	72.7%	<0.001
	Vildagliptin	5	4.1%	14	23.0%	19	10.4%	
	Sitagliptin	14	11.5%	10	16.4%	24	13.1%	
	Linagliptin	3	2.5%	3	4.9%	6	3.3%	
	Saxagliptin	0	0.0%	1	1.6%	1	0.5%	
Co-treatments	Diuretics	69	56.6%	28	45.9%	97	53.0%	0.17
	Antihypertensives/ antiarrhythmic agents	101	82.8%	47	77.0%	148	80.9%	0.36
	Neuroleptics	46	37.7%	26	42.6%	72	39.3%	0.52
	Antiaggregants/ anticoagulants	85	69.7%	45	73.8%	130	71.0%	0.56
	NSAIDs	12	9.8%	0	0.0%	12	6.6%	0.14
	Analgesics	22	18.0%	12	19.7%	34	18.6%	0.79
	Statins	71	58.2%	31	50.8%	102	55.7%	0.34
	Antihistamines	5	4.1%	19	31.1%	24	13.1%	<0.001
	Anti-diabetics**	122	100.0%	51	83.6%	173	94.5%	0.08
	Endocrine or metabolic treatment***	45	36.9%	27	44.3%	72	39.3%	0.32
	Proton pump inhibitors	59	48.4%	28	45.9%	87	47.5%	0.75
Others	50	41.0%	23	37.7%	73	39.9%	0.67	

373 ** except for DPP4i

374 *** except for diabetes

375 **Table 3** - Univariate and multivariate analysis of the association between DPP4i use and BP
 376 in diabetic patients, overall and in strata of gender and age group
 377

Strata	DPP4i use	Controls		Cases		Univariate analysis*		Multivariable analysis**	
		N	%	N	%	OR (95% CI)	p	OR (95% CI)	p
Overall	No	100	82.0%	33	54.1%	1		1	
	Yes	22	18.0%	28	45.9%	3.45 (1.76 - 6.77)	<0.001	2.64 (1.19 - 5.85)	0.02
Overall (detailed)	No	100	82.0%	33	54.1%	1		1	
	Vildagliptin	5	4.1%	14	23.0%	7.23 (2.44 - 21.40)	<0.001	3.57 (1.07 - 11.84)	0.04
	Sitagliptin	14	11.5%	10	16.4%	1.82 (0.73 - 4.54)	0.20	2.13 (0.77 - 5.89)	0.15
	Linagliptin/Saxagliptin	3	2.5%	4	6.6%	5.10 (0.98 - 26.62)	0.053	2.90 (0.47 - 17.74)	0.25
Males	No	51	85.0%	13	43.3%	1		1	
	Yes	9	15.0%	17	56.7%	5.85 (2.13 - 16.08)	0.001	4.36 (1.38 - 13.83)	0.01
Females	No	49	79.0%	20	64.5%	1		1	
	Yes	13	21.0%	11	35.5%	2.00 (0.78 - 5.15)	0.15	1.64 (0.53 - 5.11)	0.39
Age <80 yrs	No	49	79.0%	18	56.2%	1		1	
	Yes	13	21.0%	14	43.8%	2.47 (1.00 - 6.13)	0.05	1.53 (0.52 - 4.52)	0.44
Age ≥80 yrs	No	51	85.0%	15	51.7%	1		1	
	Yes	9	15.0%	14	48.3%	4.50 (1.58 - 12.77)	0.005	5.31 (1.60 - 17.62)	0.006

378 OR: odds ratio, CI: confidence interval, yrs: years

379 * Univariate conditional logistic regression analysis

380 ** Multivariable conditional logistic regression analysis including terms for neurological,
 381 metabolic/endocrine and other dermatological comorbidities