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Oral diabetes medications other than dipeptidyl peptidase-4 inhibitors are not associated with bullous pemphigoid: a Finnish nationwide case control study

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Capsule summary:

Dipeptidyl peptidase-4 inhibitor (DPP-4i) medication increases the risk of bullous pemphigoid.

In this case control study from a Finnish patient registry, conventional oral anti-diabetic medications were not associated with increased risk of bullous pemphigoid.

Diabetes medications other than DPP-4i may be safe to use in patients with bullous pemphigoid.

ABSTRACT

Background: Dipeptidyl peptidase-4 inhibitors (DPP-4i) used to treat diabetes have been reported to be associated with an increased risk of bullous pemphigoid (BP). There are no previous reports analyzing the risk of BP in patients using other diabetes medications.

Objective: To evaluate the association between diabetes medications other than DPP-4i and development of BP.

Methods: We investigated prevalence of diabetes among BP patients, and the association between the use of diabetes drugs (excluding DPP-4i, metformin and insulin) and BP, by analyzing national Finnish registry data for 3397 BP patients and 12941 basal cell carcinoma patients as controls.

Results: Our results show that 19.6% of BP patients have type 2 diabetes. The use of none of the investigated medications was associated with an increased risk for BP.

Limitations: Since this was a registry-based study, it was not possible to verify the accuracy of the diagnoses. The risk of BP in users of glucagon-like peptide-1 receptor agonists could not be analyzed.

Conclusion: Our study shows that the investigated diabetes drugs are not associated with increased risk of BP in a Finnish patient-base, indicating they can be safely used in this population. Generalization of these results to other populations will require further study.

1 INTRODUCTION

2 Bullous pemphigoid (BP) is the most common autoimmune blistering skin disease, which mainly
3 affects people in their late 70s. (1). BP patients tend to be multimorbid: in a recent study 84% of
4 subjects with BP also had at least two other chronic diseases (2). Reports of the prevalence of
5 diabetes among BP patients vary between eight and 40% (Supplementary table I), and it is among
6 the three commonest comorbidities in BP patients (2). Polypharmacy is common among BP
7 patients and appears to be associated with heightened mortality (3). Several medications are
8 suspected to predispose for BP (4). Most recently, dipeptidyl peptidase 4 inhibitors (DPP-4i), a
9 class of oral anti-hyperglycemic drugs used for the treatment of diabetes, have been shown to
10 increase the risk of BP significantly. The DPP-4i vildagliptin has been particularly implicated. (5-7)
11 Although national or international guidelines do not currently address this issue, the recent data
12 suggests that DPP-4i should not be used in patients with BP (5,7). In our previous study, the use of
13 metformin was not associated with increased risk for BP (5). However, given the common
14 comorbidity between BP and diabetes (2) it is of great importance to identify any risks of other
15 classes of diabetes medication in patients with BP.

17 METHODS

18 *Populations and databases*

19 This was a retrospective registry study of all patients diagnosed with BP in Finland between 1st
20 January 1997 and 31st Dec 2013. Patient records were obtained from the Finnish Care Register for

21 Heath Care (formerly named the Hospital Discharge Register), which contains data on the diagnosis
22 codes of hospitalized inpatients from the year 1994 onwards and of outpatient visits from 1998
23 onwards. Data for the Care Register are collected from all hospitals maintained by local authorities,
24 municipal federations, central government and also from the largest private hospitals. Similarly to
25 our previous study (8), patients were selected by a diagnosis of BP: ICD 9 codes 6945A and 6945B,
26 ICD 10 code L12.0. The control population in this study was constructed from patients diagnosed
27 with basal cell carcinoma (BCC): ICD 9 codes 1730A-1739A and ICD 10 codes C44.01, C44.11,
28 C44.21, C44.31, C44.41, C44.51, C44.61, C44.71, C44.81 and C44.91. For each BP case, four
29 controls were randomly selected from the BCC control group, and matched by sex, age and year of
30 diagnosis (within 2 years). For both BP and BCC, we used the first diagnosis that was found in the
31 database. We also collected data on all subjects' other diagnoses. All patients aged under 40 years
32 were excluded from the study since BP is rare in younger age groups (1).

33

34 Data on drugs used by patients in both groups were obtained from the database of Social Insurance
35 Institution of Finland. The nationwide registry includes reliable data on all drugs reimbursed from
36 the year 1995 onwards. Therefore, to obtain data on all reimbursed drugs for two years prior to BP
37 or BCC diagnosis, only patients diagnosed between the years 1997 and 2013 were included in the
38 present study. The unique personal identification number given to every Finnish citizen was used to
39 combine the data from the Care Register and the Social Insurance databases. Drugs were classified
40 according to the Anatomical Therapeutic Chemical (ATC) classification system and data were
41 collected using ATC-codes. Diabetes drugs were classified by pharmacological subgroups:
42 sulfonylureas (A10BB), heterocyclic sulfonamides (A10BC), combinations of oral glucose-
43 lowering drugs (A10BD), alpha glucosidase inhibitors (A10BF), thiazolidinediones (A10BG),
44 glucagon-like peptide-1 (GLP-1) analogues (A10BJ), Sodium-glucose co-transporter 2 inhibitors
45 (A10BK) and other blood glucose lowering drugs, excluding insulins (A10BX). Every drug in each

of these subgroups was also examined individually. Since metformin, DPP-4i and insulin preparations were not to be included in the present analysis, records for patients receiving metformin, DPP-4i or insulin monotherapy or in combinations, were excluded. Where data were examined by drug class, the observation period started from the date of the approval in Finland of the first available drug in the class. The dates of approval were obtained from the website of the Finnish Medicines Agency Fimea (www.fimea.fi).

Statistical analysis

The characteristics of the study population are presented as proportions and means. The associations between diabetes drugs and BP were evaluated using a conditional logistic regression model and presented with odds ratios (ORs) and 95% confidence intervals (CIs). All Statistical analyses were performed using the SAS software package (version 9.4, SAS Institute, Inc). Two-sided P-values less than 0.05 were considered statistically significant.

RESULTS

The database search returned records for 4524 patients with BP who were treated in Finnish hospitals between the years 1987 and 2013. The present analysis included a subgroup of 3397 BP cases diagnosed with BP between the years 1997 and 2013. A total of 66138 cases of BCC were identified. Of these 12941 were randomly selected to comprise the control group and were matched by age, sex and year of diagnosis to the BP group in a 4:1 ratio. Due to the absence of drug reimbursement data of some of the BCC controls, 579 BP patients had fewer than four controls.

Both type 1 and type 2 diabetes were significantly more common in the BP patients than in the controls (Table I). Due to unspecific diagnosis codes used some cases were classified as diabetes of unspecified type.

In total, 582 (17.1%) of BP patients and 1555 (12.0%) of controls had used at least one diabetes medication other than insulin. After adjusting for diabetes and several neurological diseases no association with BP risk was found for metformin-thiazolidinedione combination therapy regimens, sulfonylureas, thiazolidinediones, or “other diabetes drugs” (guar gum, repaglinide) (Table II). No heightened risk was seen when patient data were stratified by sex (Supplementary Table II).

DISCUSSION

Previous studies reporting the prevalence of diabetes in BP patients were mainly based on hospital data (Supplementary Table I). Our results are in line with a Danish population-based study, in which diabetes was found in 23% of BP cases (9). However, we found type 1 diabetes to be much less common (0.9% patients) than in the Danish study (7.1%). There are no other studies reporting the exact prevalence of type 1 diabetes in BP patients, since the type of diabetes was mostly unspecified in the study from United States (10).

To best of our knowledge, no previous nationwide registry study has shown that conventional oral antidiabetics are not associated with an increased risk for BP (See Supplementary material for literature search strategy). Previously, diabetes medications other than DPP-4i have only been studied as a small part of a British study, in which 10.5% (N=9) of BP patients were on “oral hypoglycemics” compared to 4.5% (N=6) of controls (4). A hospital based Singaporean study reported that 4.8% (N=5) of BP patients used either sulfonylurea, metformin or acarbose compared to 7.0% (N=22) of controls, but newer diabetes medications like DPP-4i were not analysed (11).

In general, BP occurs more often in women than in men (1). In this study, no sex differences were found in the risk for developing BP after diabetes medication exposure. Studies of DPP-4i associated risk for BP are contradictory: a hospital-based Swiss-French study found an greater risk among males (7). By contrast, our recent Finnish nationwide registry study found a three-fold greater risk for BP in women using any DPP-4i compared with men, and a trend towards a heightened risk in women using vildagliptin (5).

EudraVigilance is a database of the European Medicines Agency where suspected adverse drug reactions (ADRs) reported by national medicines regulatory authorities and pharmaceutical companies are collected. In the EudraVigilance database (by February 2018), 0–3.8 % of all skin and subcutaneous tissue related ADRs reported by health care professionals concerning conventional oral antidiabetics and injectable incretin mimetics were classified as pemphigoid (Supplementary table III). In contrast, 51% of reported skin and subcutaneous tissue related ADRs concerning vildagliptin were pemphigoid. Thus, the data obtained from EudraVigilance aligns with our results (<http://www.adrreports.eu/>).

Recent studies have added to our knowledge of the association between DPP-4i medication use and BP risk (5-7). Currently it is not known whether DPP-4i-associated BP is a drug-induced or rather a drug aggravated condition (5) although in some cases, clinical remission of BP has been reported following DPP-4i withdrawal (7). When an adverse drug reaction is suspected, the medications that is a candidate cause should be withdrawn. This often presents a complex scenario for the clinician treating comorbid BP and diabetes, since the oral corticosteroids often used to treat moderate to severe BP (1) tend to elevate blood glucose. It has been shown that metformin monotherapy is not associated with increased risk for BP (5). However, if the DPP-4i treatment is withdrawn, metformin alone may not be sufficient to control hyperglycemia in these patients (12). Our results suggest that other classes of oral antidiabetics can be used as a substitute for DPP-4i without risk of further aggravating BP symptoms.

115 A major strength of our study is availability in the records of the Social Insurance Institution of
116 Finland of information on reimbursed medication that patients have purchased. Another major
117 strength is that our study utilized one of the largest ever nationwide BP cohorts (13).

118 The present study has some limitations. Because we utilized routinely collected registry data we
119 have no certainty that all the BP cases were immunologically confirmed and no information
120 regarding the timing of the onset of the BP symptoms. Patients without blistering or extensive
121 symptoms may have been misdiagnosed it was not possible to analyze any the relationship between
122 GLP-1 and BP due to few patients using these medications. The use of patients with BCC as a
123 control population may have introduced some confounding factors since compared with age- and
124 sex- matched BCC controls, BP patients are more likely to have diabetes.

125 In conclusion, our study shows that the investigated diabetes drugs are not associated with increased
126 risk of BP in a Finnish patient-base, indicating they can be safely used in this population.
127 Generalization of these results to other populations will require further studies.

128

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Abbreviations used:

ATC: Anatomical Therapeutic Chemical

BCC: basal cell carcinoma

BP: bullous pemphigoid

CI: confidence interval

DPP-4i: Dipeptidyl peptidase-4 inhibitor

ICD: International Classification of Diseases

OR: odds ratio

Table I. Diabetic cases in bullous pemphigoid (BP) group and basal cell carcinoma (BCC) control group

Group	Total (N)	DM 1^a % (N)	DM 2^b % (N)	Unspecified DM^c type % (N)
BP	4524	0.93 (42)	19.6 (887)	0.35 (16)
BCC	66138	0.50 (329)	12.3 (8111)	0.18 (118)

^adiabetes mellitus type 1

^bdiabetes mellitus type 2

^cdiabetes mellitus

Table II. Antidiabetic drugs used by bullous pemphigoid cases and basal cell carcinoma controls and Odds Ratios for bullous pemphigoid risk

Drug	Group	Total ^a	N (%)	Crude OR (95% CI)	Adjusted OR (95% CI) ^b	Adjusted OR (95% CI) ^c
Sulfonylureas	Cases	3397	231 (6.8)	1.46 (1.25 - 1.71)	0.96 (0.77 - 1.19)	0.99 (0.79 - 1.25)
	Controls	12941	620 (4.8)	Reference	Reference	Reference
Glipizide	Cases	3397	36 (1.1)	1.50 (1.01 - 2.22)	1.57 (0.89 - 2.76)	1.63 (0.91 - 2.89)
	Controls	12941	90 (0.7)	Reference	Reference	Reference
Glimepiride	Cases	3360	197 (5.9)	1.44 (1.22 - 1.70)	0.89 (0.71 - 1.13)	0.93 (0.73 - 1.18)
	Controls	12884	538 (4.2)	Reference	Reference	Reference
Combinations of oral blood glucose lowering drugs^d						
Metformin and rosiglitazone	Cases	2512	11 (0.4)	1.38 (0.69 - 2.77)	1.96 (0.89 - 4.31)	1.96 (0.89 - 4.33)
	Controls	10072	31 (0.3)	Reference	Reference	Reference
Metformin and pioglitazone	Cases	2060	5 (0.2)	2.02 (0.67 - 6.08)	3.21 (0.71 - 14.50)	3.03 (0.65 - 14.10)
	Controls	6989	9 (0.1)	Reference	Reference	Reference
Thiazolidinediones	Cases	2980	28 (0.9)	1.89 (1.20 - 2.97)	1.14 (0.63 - 2.08)	1.16 (0.63 - 2.12)
	Controls	11741	59 (0.5)	Reference	Reference	Reference
Rosiglitazone	Cases	2980	8 (0.3)	1.12 (0.51 - 2.47)	0.47 (0.15 - 1.45)	0.47 (0.15 - 1.45)
	Controls	11741	28 (0.2)	Reference	Reference	Reference
Pioglitazone	Cases	2940	20 (0.7)	2.55 (1.45 - 4.48)	1.74 (0.87 - 3.50)	1.78 (0.87 - 3.63)
	Controls	11601	31 (0.3)	Reference	Reference	Reference
Glucagon-like peptide-1 (GLP-1) analogues	Cases	1979	1 (0.1)			
	Controls	7824	4 (0.1)			
Exenatide	Cases	1979	1 (0.1)			
	Controls	7824	1 (0.0)			
Liraglutide	Cases	1373	0 (0.0)			
	Controls	5429	4 (0.1)			

Other blood glucose lowering drugs, excl. insulins	Cases	3397	29 (0.9)	1.61 (1.04 - 2.49)	0.97 (0.56 - 1.65)	0.95 (0.55 - 1.63)
	Controls	12941	69 (0.5)	Reference	Reference	Reference
Guar gum	Cases	3397	18 (0.5)	1.28 (0.75 - 2.20)	0.91 (0.48 - 1.72)	0.89 (0.47 - 1.69)
	Controls	12941	53 (0.4)	Reference	Reference	Reference
Repaglinide	Cases	3239	11 (0.3)	2.56 (1.20 - 5.47)	0.93 (0.34 - 2.56)	1.07 (0.37 - 3.12)
	Controls	12756	17 (0.1)	Reference	Reference	Reference

^a Including cases and controls diagnosed after the drug in question had been approved for use in Finland

^b OR adjusted for diabetes

^c OR adjusted for diabetes, Alzheimer's disease, vascular dementia, other/unspecified dementia, Parkinson's disease, multiple sclerosis, subarachnoid hemorrhage, intracerebral hemorrhage, cerebral infarction and epilepsy.

^d excluding dipeptidyl peptidase 4-inhibitor

Supplementary material

Literature search method

We conducted a literature search in PubMed (from 1947 to 13th of March 2018) using Medical Subject Headings (MeSH) terms “Bullous pemphigoid” and “Diabetes mellitus” or “Hyperglycemia”. The screen of the titles removed clearly irrelevant articles. To be examined further, abstracts of remaining articles were read to determine relevance. Original studies discussing BP, comorbidities and drugs used were included. In addition, manual review of reference lists of certain articles such as recent reviews on the field of BP were undertaken to identify additional publications for consideration. The search was conducted independently by two authors to ensure reproducibility.

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Supplementary Table I. Prevalence of diabetes among bullous pemphigoid patients.

First author	Year	Data of origin	Number of cases (N)	Unspecified type %	Type 1 diabetes %	Type 2 diabetes %
Roujeau (1)	1998	France, hospital data	217	9.3		
Parker (2)	2008	USA, laboratory database	223	11.7		
Jedlickova (3)	2010	Czech, hospital data	89	34.8		
Cortes (4)	2011	Switzerland, national data	115	8.2		
Bastuij-Garin (5)	2011	French, hospital data	201	6.0		
Gual (6)	2012	Spain, hospital data	101	22.7		
Cortes (7)	2012	Switzerland, Italy hospital data	60	10.2		
Li (8)	2013	China, hospital data	140	15.0		
Cai (9)	2014	Singapore, hospital data	359	6		
Teixeira (10)	2014	Portugal, hospital data	77	26.0		
Försti (11)	2016	Finland, hospital data	198			23.2
Ren (12)	2017	USA, NIS data	2108 ^a 11234 ^b	20.3 ^c	0.14	1.71
Sim (13)	2017	Singapore, hospital data	105	40.0		
Kibsgaard (14)	2017	Denmark, population study	3281		7.1.	16.0

^aPrimary diagnose of bullous pemphigoid^bSecondary diagnose of bullous pemphigoid^ccomplicated and uncomplicated diabetes classified as separate diagnosis, types not specified (not included)

Drug	Sex		Group	Total ^a	N (%)	Crude OR (95% CI)	Adjusted OR (95% CI) ^b	Adjusted OR (95% CI) ^c
Sulfonylureas		Male	Cases	1369	104 (7.6)	1.58 (1.24 - 2.00)	0.79 (0.56 - 1.12)	0.83 (0.58 - 1.19)

Supplementary Table II. Differences between genders using antidiabetics other than metformin or dipeptidyl peptidase 4-inhibitor and Odds Ratios for bullous pemphigoid.

Glipitazide	Female	Controls	5175	261 (5.0)	Reference	Reference	Reference
		Cases	2028	127 (6.3)	1.38 (1.12 - 1.70)	1.09 (0.82 - 1.46)	1.12 (0.84 - 1.50)
		Controls	7766	359 (4.6)	Reference	Reference	Reference
	Male	Cases	1369	15 (1.1)	2.12 (1.12 - 4.02)	1.37 (0.43 - 4.37)	1.24 (0.37 - 4.10)
		Controls	5175	27 (0.5)	Reference	Reference	Reference
	Female	Cases	2028	21 (1.0)	1.23 (0.74 - 2.03)	1.53 (0.79 - 2.98)	1.62 (0.83 - 3.18)
Controls		7766	63 (0.8)	Reference	Reference	Reference	
Glimepiride	Male	Cases	1353	89 (6.6)	1.49 (1.16 - 1.92)	0.73 (0.51 - 1.05)	0.77 (0.53 - 1.11)
		Controls	5154	236 (4.6)	Reference	Reference	Reference
	Female	Cases	2007	108 (5.4)	1.40 (1.12 - 1.76)	1.05 (0.77 - 1.44)	1.07 (0.78 - 1.47)
		Controls	7730	302 (3.9)	Reference	Reference	Reference
Combinations of oral glucose lowering drugs							
Metformin and rosiglitazone	Male	Cases	1036	9 (0.9)	2.47 (1.07 - 5.72)	3.85 (1.39 - 10.7)	3.75 (1.35 - 10.5)
		Controls	4076	14 (0.3)	Reference	Reference	Reference
	Female	Cases	1476	2 (0.1)	0.46 (0.10 - 1.99)	0.57 (0.12 - 2.75)	0.53 (0.11 - 2.63)
		Controls	5996	17 (0.3)	Reference	Reference	Reference
Metformin and pioglitazone	Male	Cases	844	4 (0.5)	2.78 (0.73 - 10.5)	9.03 (0.96 - 85.1)	8.89 (0.93 - 84.8)
		Controls	3333	6 (0.2)	Reference	Reference	Reference
	Female	Cases	1216	1 (0.1)	1.00 (0.11 - 8.95)	0.00 (0.00 - .)	0.00 (0.00 - .)
		Controls	4820	4 (0.1)	Reference	Reference	Reference
Thiazolidinediones	Male	Cases	1208	15 (1.2)	2.57 (1.34 - 4.92)	1.74 (0.75 - 4.02)	1.72 (0.74 - 4.01)
		Controls	4692	23 (0.5)	Reference	Reference	Reference
	Female	Cases	1772	13 (0.7)	1.44 (0.76 - 2.73)	0.77 (0.33 - 1.83)	0.78 (0.33 - 1.87)
		Controls	7049	36 (0.5)	Reference	Reference	Reference
Rosiglitazone	Male	Cases	1208	2 (0.2)	0.80 (0.18 - 3.65)	1.09 (0.15 - 8.02)	1.09 (0.14 - 8.66)
		Controls	4692	10 (0.2)	Reference	Reference	Reference
	Female	Cases	1772	6 (0.3)	1.30 (0.52 - 3.28)	0.35 (0.09 - 1.39)	0.32 (0.07 - 1.36)
		Controls	7049	18 (0.3)	Reference	Reference	Reference
Pioglitazone	Male	Cases	1189	13 (1.1)	3.91 (1.81 - 8.45)	2.19 (0.85 - 5.65)	2.24 (0.83 - 6.02)
		Controls	4641	13 (0.3)	Reference	Reference	Reference
	Female	Cases	1751	7 (0.4)	1.56 (0.65 - 3.72)	1.41 (0.49 - 4.10)	1.41 (0.48 - 4.11)
		Controls	6960	18 (0.3)	Reference	Reference	Reference
Glugacon like peptiden-1 (GLP-1) analogues	Male	Cases	811	1 (0.1)			
		Controls	3211	2 (0.1)			
	Female	Cases	1168	0 (0.0)			
		Controls	4613	2 (0.0)			
Exenatide	Male	Cases	811	1 (0.1)			
		Controls	3211	0 (0.0)			
	Female	Cases	1168	0 (0.0)			
		Controls	4613	1 (0.0)			

Liraglutide	Male	Cases	577	0 (0.0)			
		Controls	2248	2 (0.1)			
	Female	Cases	796	0 (0.0)			
		Controls	3181	2 (0.1)			
Other blood glucose lowering drugs, excl. insulins	Male	Cases	1369	11 (0.8)	1.62 (0.80 - 3.28)	1.36 (0.52 - 3.55)	1.42 (0.54 - 3.73)
		Controls	5175	26 (0.5)	Reference	Reference	Reference
	Female	Cases	2028	18 (0.9)	1.61 (0.92 - 2.80)	0.86 (0.44 - 1.66)	0.83 (0.42 - 1.62)
		Controls	7766	43 (0.6)	Reference	Reference	Reference
Guar gum	Male	Cases	1369	5 (0.4)	0.98 (0.36 - 2.63)	1.09 (0.34 - 3.51)	1.09 (0.34 - 3.50)
		Controls	5175	19 (0.4)	Reference	Reference	Reference
	Female	Cases	2028	13 (0.6)	1.46 (0.77 - 2.78)	0.85 (0.40 - 1.83)	0.81 (0.37 - 1.77)
		Controls	7766	34 (0.4)	Reference	Reference	Reference
Repaglinide	Male	Cases	1303	6 (0.5)	3.00 (1.04 - 8.65)	1.10 (0.23 - 5.32)	2.08 (0.28 - 15.2)
		Controls	5102	8 (0.2)	Reference	Reference	Reference
	Female	Cases	1936	5 (0.3)	2.18 (0.73 - 6.50)	0.84 (0.21 - 3.33)	0.86 (0.21 - 3.46)
		Controls	7654	9 (0.1)	Reference	Reference	Reference

^a Including cases and controls diagnosed after the drug in question had been approved for use in Finland

^b OR adjusted for diabetes

^c OR adjusted for diabetes, Alzheimer's disease, vascular dementia, other/unspecified dementia, Parkinson's disease, multiple sclerosis, subarachnoid hemorrhage, intracerebral hemorrhage, cerebral infarction and epilepsy.

Supplementary table III. Suspected adverse drug reactions reported by health care professionals by February 2018 in EudraVigilance (European database of suspected adverse drug reaction reports).

Medication	Suspected pemphigoid (N)	All suspected ADRs ^a related to skin and subcutaneous tissue (N)	Suspected pemphigoid of all suspected ADRs related to skin and subcutaneous
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			tissue (%)
Glipizide	0	88	0
Glimepiride	14	430	3.25
Metformin and rosiglitazone	1	60	1.67
Metformin and pioglitazone	0	28	0
Rosiglitazone	0	282	0
Pioglitazone	5	264	1.89
Exenatide	8	687	1.16
Liraglutide	4	336	1.19
Guar gum	-	-	-
Repaglinide	8	210	3.81

^aAdverse drug reaction