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ORIGINAL ARTICLE

Therapy with proton pump inhibitors in patients with type 2 diabetes is independently associated with improved glycometabolic control

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Abstract
Aims Experimental data demonstrated that gastrin has incretin-like stimulating actions on β-cells, resulting in a promotion of glucose–induced insulin secretion. As proton pump inhibitors (PPIs) consistently increase plasma gastrin levels, a possible effect of this treatment on glucose–insulin homeostasis may be hypothesized. Therefore, the aim of this study was to evaluate the effect of chronic PPIs treatment on glycemic control in patients affected by type 2 diabetes.
Methods This is an observational, retrospective study. A total of 548 consecutive patients with type 2 diabetes (mean age ± SD: 67.1 ± 10.9 years, *M*/*F*: 309/239, diabetes duration: 12.4 ± 9.8 years) referring to our diabetes outpatient clinics were enrolled; among them, 45 %were treated with PPIs longer than 2 years for preventive/therapeutic purposes. Fasting plasma glucose (FPG), glycated hemoglobin (HbA1c), serum lipids and transaminases were measured by standard laboratory methods. Major cardiovascular events and concomitant medications were recorded in all participants, and daily insulin requirement was calculated in insulin-treated subjects.
Results PPIs-treated patients had significantly lower HbA1c (7.1 ± 1.07 %–54.1 ± 12 vs 7.4 ± 1.4 %–57.4 ± 8 mmol/mol, $p = 0.011$) and FPG (127 ± 36.9 vs 147.6 ± 49.4 mg/dl, $p < 0.001$) levels than those untreated. These differences increased in patients under insulin therapy and in those with concomitant PPIs + GLP-1-based therapy. The multivariate regression analysis demonstrated that the association between chronic PPIs treatment and HbA1c was independent from possible confounders ($p = 0.01$).
Conclusions PPIs treatment is associated with greater glycemic control in patients with type 2 diabetes, particularly in those on insulin- or GLP-1-based therapy. Our results suggest a role for PPIs in glucose–insulin homeostasis and may open a new scenario for diabetes therapy.

Keywords Type 2 diabetes · Therapy · Incretins · PPI

Introduction

Proton pumps inhibitors (PPIs) represent a class of drugs widely used for treatment and prevention of gastroesophageal reflux disease and gastritis, gastroduodenal ulcer, drug-induced ulcers and healing of erosive esophagitis. They inhibit H^+ K^+-ATPase in gastric parietal cells, leading to drastic reduction in acid secretion into the stomach [1, 2] and, as a consequence, to strongly increased levels of gastrin which, in physiological conditions, stimulates acid secretion by gastric parietal cells [3–6].

Managed by Massimo Porta.

A complete list of investigators can be found in the Online Appendix.

Ilaria Barchetta and Chiara Guglielmi have contributed equally to this work.

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Moreover, experimental data obtained in rodents demonstrated that gastrin promotes the neogenesis and expansion of pancreatic β-cells [7, 8] and displays on them an incretin-like action, stimulating the glucose-induced insulin secretion [9]. In addition, it has been proven that PPIs treatment modulates somatostatin levels and delays gastric emptying, likely playing an overall beneficial effect on glucose metabolism [10–12].

Very recent clinical studies investigated the association between chronic PPIs treatment and glycemic control in small cohorts of subjects affected by diabetes, obtaining conflicting results [13–18].

Therefore, the aim of this study was to investigate the presence of an association between chronic PPIs treatment and glycemic control in a large population of adult patients affected by type 2 diabetes. In particular, we studied the additional effect of PPIs therapy on coexistent antidiabetic treatment, including insulin- and GLP-1-based agents, on fasting blood glucose (FBG) and glycated hemoglobin (HbA1c) in a large and extremely well-characterized population of patients with type 2 diabetes with and without comorbidities and cardiovascular disease.

Research design and methods

Population

This is an observational, retrospective study considering 548 consecutive patients affected by type 2 diabetes (mean age ± SD: 67.1 ± 10.9 years, *M*/*F*: 309/239, diabetes duration: 12.4 ± 9.8 years) referring to Diabetes outpatient clinics of Sapienza University and University Campus Bio-Medico in Rome. To be eligible for the study, patients had to fulfill the following criteria: diagnosis of type 2 diabetes according to ADA 2009 criteria, no history of current malignancies, systemic or local infections, chronic hepatic or end-stage renal disease or treatment with H2 receptor blockers.

For each patient, we collected and analyzed data on medical history, physical examination [Body Mass Index (BMI, Kg/m^2), systolic and diastolic blood pressure (SBP, DBP and mmHg)], biochemistry, diabetes complications and the occurrence of major cardiovascular events [chronic ischemic coronary disease, history of acute myocardial infarction (AMI) and stroke]. Antidiabetic therapy and concomitant medications were specifically recorded, and daily insulin requirement (IR, IU/Kg/day) was calculated in insulin-treated subjects.

Patients were considered under PPIs treatment when taking PPIs continuously for longer than 2 years before data collection; information about reason for prescription (symptoms of gastroesophageal reflux disease and gastritis, treatment/prevention of peptic and drug-induced ulcers and healing of erosive esophagitis), type of active molecule of PPIs (omeprazole, esomeprazole, pantoprazole and lansoprazole) and its dosage was recorded.

Diabetic nephropathy was defined as persistent microalbuminuria (30–300 mg/day) or macroalbuminuria (>300 mg/day) in at least 2 of 3 samples collected over 24 h.

FBG (mg/dl), HbA1c (%–mmol/mol), total cholesterol (mg/dl), HDL cholesterol (mg/dl), triglycerides (mg/dl), AST (IU/l), ALT (IU/l) and γGT (IU/l) were measured by standard laboratory methods after an overnight fasting. LDL cholesterol value was obtained using Fiedwald formula.

Statistics

SPSS version 17 statistical package was used to perform the analyses. Student's *T* test for continuous variables and Chi-square test for categorical variables were used to compare mean values between two independent groups. As BMI, triglycerides, AST, ALT and γGT were skewed, we used natural logarithmic transformation to normalize the distribution of these variables before all analyses. Comparison between more than two groups was obtained by the analysis of variance (ANOVA) with post hoc Bonferroni adjustment. Bivariate and multivariate linear regression analyses were used to detect the association between serum HbA1c measurement, considered as a continuous variable, and all possible determinants. Correlations between continuous variables were calculated by Pearson's coefficient, whereas Spearman's was used for ordinal/binomial parameters. A multiple liner regression analysis, sex- and age-forced, was performed to confirm the independence of the association between HbA1c (considered as dependent variable) and clinical and biochemical parameters significantly associated at the bivariate analysis. Data are shown as mean ± SD or as percentage, appropriately. For all the above, a p value <0.05 was considered statistically significant.

The study protocol was reviewed and approved by the Ethics Committee at Policlinico Umberto I, Sapienza University of Rome, and conducted in conformance with the Helsinki Declaration. Written consent was obtained from all patients before the study.

Results

Out of 548 patients enrolled for this study, 245 (45 %) were chronically treated with PPIs as described before, whereas 303 were not treated with PPIs in the 2 years preceding enrollment. Characteristics of the whole study sample are shown in Table 1.

Patients on PPIs treatment had significantly lower HbA1c (7.1 ± 1.07 %–54.1 ± 8 mmol/mol, vs 7.4 ± 1.4 %–57.4 ± 12 mmol/mol, $p = 0.011$) and FPG (127 ± 36.9 mg/dl vs 147.6 ± 49.4 mg/dl, $p < 0.001$) levels than those untreated. Although PPI-treated patients were significantly older than patients belonging to the PPIs-untreated group (mean age ± SD: 69.3 ± 9.6 and 65.3 ± 11.5 years, respectively; $p < 0.001$), diabetes duration between the two subgroups was comparable. The rate of major cardiovascular events, and thus of chronic salicylate therapy, was significantly greater in PPIs-treated patients in comparison with that reported in non-PPIs-treated diabetic subjects. Clinical and biochemical characteristics of study population according to the presence or absence of chronic PPI treatment are listed in Table 2.

In order to investigate the effect of PPIs treatment on glycemic control according to the current antidiabetic therapy, we performed distinct sub-analyses considering separately: (I) patients with insulin therapy and (II) patients treated with drugs acting on incretin axis (GLP-1 agonists/DPP-IV inhibitors).

Table 1 Clinical and biochemical parameters of study population

Clinical and biochemical parameters	
Subjects	548
Age (years)	67.1 ± 10.9
Sex (male vs female)	56 %
BMI (kg/m^2)	30.2 ± 5.5
SBP (mm/Hg)	135 ± 16.2
DBP (mm/Hg)	81 ± 9.1
Diabetes duration (years)	12.4 ± 9.8
HbA_1C (%, mmol/mol)	7.26 ± 1.3, 55.8 ± 9.2
FBG (mg/dl)	139.26 ± 46.7
Total cholesterol (mg/dl)	172.5 ± 42.3
HDL cholesterol (mg/dl)	49.5 ± 15.2
LDL cholesterol (mg/dl)	96.4 ± 35.1
Triglycerides (mg/dl)	143.9 ± 96
AST (IU/l)	21.5 ± 12.1
ALT (IU/l)	26.2 ± 16.1
γ-GT (IU/l)	40.5 ± 39.5
Insulin therapy (%)	35
Ischemic coronary disease (%)	13
Acute myocardial infarction (%)	7
Insulin requirement (IU/Kg/die)	0.6 ± 0.38
Microalbuminuria (mg/l)	16.9 ± 33
Antihypertensive therapy (%)	67
Statin therapy (%)	64
Salicylate therapy (%)	52
PPIs therapy (%)	45

Results are expressed as mean value ± SD or percentage (%) as appropriate

PPIs + insulin therapy

After stratifying the study sample according to the concomitant use of insulin ($n = 192$), we found that patients on insulin therapy plus PPIs ($n = 92$) had significantly better glycemic control than subjects treated with insulin without chronic PPIs therapy (insulin + PPIs-treated group HbA1c: 7.6 ± 1 %–60 ± 8 mmol/mol, FBG: 144.5 ± 41.5 mg/dl; insulin treated without PPIs group HbA1c: 8.2 ± 1.6 %–66 ± 12 mmol/mol, FBG: 177.1 ± 64.4 mg/dl, p value = 0.002, 0.013, respectively).

However, among patients treated with antidiabetic agents but insulin ($n = 356$), subjects using PPIs ($n = 153$) had significantly lower FBG than those untreated ($n = 203$) with comparable HbA1c levels between the two subgroups, although slightly lower in patients on PPIs therapy.

The features of study populations on insulin therapy or treated with antidiabetic drugs other than insulin, with or without therapy with PPIs, are shown in Tables 3 and 4.

PPIs + incretin-based therapy

We identified a subgroup of patients on incretin-based therapy ($n = 116$) and found that subjects undertaking incretin + PPIs therapy ($n = 47$) had lower HbA1c and FBG levels than those reported in patients treated with incretins without PPIs ($n = 69$) (incretins + PPIs-treated group HbA1c: 6.8 ± 0.8 %–51 ± 6 mmol/mol, FBG: 118 ± 22.9 mg/dl; incretin therapy without PPIs group HbA1c: 7.4 ± 1.4 %–57 ± 11 mmol/mol, FBG: 148 ± 39.1 mg/dl, p value = 0.003, <0.001, respectively). With the exception of mean age (incretins + PPIs: 66.1 ± 9.1 years vs incretins without PPIs 61.6 ± 12.1 years, $p = 0.02$), these subgroups were comparable for other clinical and metabolic characteristics such as diabetes duration, BMI and concomitant medications (data not shown). Notably, the differences in glycometabolic control between patients treated or not with PPIs in addition to antidiabetic therapy were much more marked in subjects using GLP-1 agonists (GLP-1 agonist + PPIs-treated group ($n = 15$) mean HbA1c: 6.8 ± 0.9 %–51 ± 6 mmol/mol, FBG: 112.4 ± 27.4 mg/dl; GLP-1 agonist therapy without PPIs group (25) mean HbA1c: 8.1 ± 1.4 %–65 ± 11 mmol/mol, FBG: 174 ± 47.6 mg/dl, p value = 0.002, <0.001, respectively) compared to those observed in patients in treatment with DPP-IV inhibitors (DPP-IV inhibitor + PPIs-treated group ($n = 32$) mean HbA1c: 6.8 ± 0.8 %–51 ± 6 mmol/mol, FBG: 120.7 ± 20.6 mg/dl; DPP-IV inhibitor without PPIs group ($n = 44$) mean HbA1c: 7 ± 1.1 %–53 ± 8 mmol/mol, FBG: 135.8 ± 29.2 mg/dl, p value = ns, 0.007, respectively).

Table 2 Clinical and biochemical characteristics of study population according to the presence (PPIs+) or absence (PPIs−) of chronic PPIs treatment

	PPIs+ ($n = 245$)	PPIs− ($n = 303$)	p value
Age (years)	69.3 ± 9.6	65.3 ± 11.5	**<0.001**
Sex (*M*/*F*)	130/114	179/125	n.s.*
BMI (kg/m^2)	30.7 ± 5.6	30.2 ± 5.5	n.s.
SBP (mm/Hg)	132.9 ± 15.7	136.2 ± 16.3	n.s.
DBP (mm/Hg)	79.5 ± 8.9	82.7 ± 9	**<0.001**
HbA_1C (%, mmol/mol)	7.1 ± 1.07, 54.1 ± 8	7.4 ± 1.4, 57.4 ± 12	**0.011**
FBG (mg/dl)	127 ± 36.9	147.6 ± 49.4	**<0.001**
Total cholesterol (mg/dl)	167.4 ± 41.5	177.3 ± 42	**0.008**
HDL cholesterol (mg/dl)	48.3 ± 16.9	50.1 ± 13.6	n.s.
LDL cholesterol (mg/dl)	93.5 ± 35.1	98.9 ± 35.5	n.s.
Triglycerides (mg/dl)	146.8 ± 75.5	141.6 ± 11.03	n.s.
AST (IU/l)	21.3 ± 11.3	22.1 ± 13.3	n.s.
ALT (IU/l)	25.2 ± 17.8	27.5 ± 15.1	n.s.
γ-GT (IU/l)	40.1 ± 40.5	43.2 ± 40	n.s.
Insulin therapy (%)	33	38	n.s.*
Ischemic coronary disease (%)	21.6	6.6	**<0.001***
Acute myocardial infarction (%)	12	3	**<0.001***
Systemic hypertension (%)	60	69	**0.016***
Insulin Requirement (IU/Kg/die)	0.58 ± 0.4	0.62 ± 0.34	n.s.
Microalbuminuria (mg/l)	17 ± 35	17.2 ± 33.6	n.s.
Diabetes duration (years)	12.9 ± 10.3	12.1 ± 9.5	n.s.
Antihypertensive therapy (%)	84	77	n.s.*
Statin therapy (%)	68	58	n.s.*
Salicylate therapy (%)	68	33	**<0.001***
Number of antidiabetic agents (% of patients in treatment)			n.s.°
No antidiabetic drugs (%)	5	3	
1 (%)	55	54	
2 (%)	32	33	
3 (%)	7	8	
4 (%)	1	2	

Significant statistical analyses are shown in bold

Results are shown as mean value ±SD or percentage (%) as appropriate. Student *T* test applied. * χ^2 test applied. ° Bonferroni post hoc-adjusted ANOVA test applied

We then performed bivariate correlation analyses which showed that HbA1c levels were associated with diabetes duration, BMI, male gender, treatment with insulin and IR. No association was found between HbA1c and age, use of antihypertensive agents, salicylate, statins, type and dosage of PPIs. HbA1c levels inversely correlated with the number of antidiabetic agents assumed but only in patients not on insulin; when insulin therapy was included in subjects' therapy, the total amount of antidiabetic medicaments did not correlate with glycemic control (Table 5).

The association between HbA1c and chronic PPIs therapy in addition to standard antidiabetic treatment was independent from all possible confounders in the multivariate linear regression analyses ($p = 0.018$) (Table 6).

Conclusions

Our results, obtained in a large population of subjects with type 2 diabetes, demonstrated that patients treated with PPIs for more than 2 years, in addition to standard antidiabetic therapy, had significantly better glycemic control, as estimated by both HbA1c and FBG, than subjects without concomitant PPIs treatment. The association between PPIs therapy and lower HbA1c levels was independent from classical determinants of glycemic control. These results were obtained in the overall population; however, when considering the subgroup of patients on insulin- or on incretin-based therapy, differences in HbA1c and FBG were even more pronounced between patients treated or not treated with PPIs.

Table 3 Patients on insulin therapy. Clinical and biochemical characteristics according to the presence (PPIs+) or absence (PPIs−) of chronic PPIs treatment

	PPIs+ ($n = 92$)	PPIs− ($n = 100$)	p value
Age (years)	71 ± 8.8	68.8 ± 10.4	n.s.
Sex (*M*/*F*)	61/31	64/36	n.s.
BMI (kg/m^2)	31.6 ± 6.4	30.1 ± 5.3	n.s.
SBP (mm/Hg)	135.1 ± 15.3	138.9 ± 16.9	n.s.
DBP (mm/Hg)	79.3 ± 9.2	81.1 ± 9	n.s.
FBG (mg/dl)	144.5 ± 41.5	177 ± 64.4	**0.013**
HbA_1C (%, mmol/mol)	7.6 ± 1, 60 ± 8	8.2 ± 1.6, 66 ± 12	**0.002**
Total cholesterol (mg/dl)	161.4 ± 43	167.4 ± 37.2	n.s.
HDL cholesterol (mg/dl)	47 ± 20.7	50.2 ± 16.2	n.s.
LDL cholesterol (mg/dl)	87.2 ± 34.8	93.5 ± 32	n.s.
Triglycerides (mg/dl)	147.7 ± 65.6	130.8 ± 84.8	n.s.
AST (IU/l)	20.8 ± 11.9	21.2 ± 18.3	n.s.
ALT (IU/l)	25.6 ± 17.8	25.4 ± 14.1	n.s.
γ-GT (IU/l)	31.5 ± 18.9	39.5 ± 35.7	n.s.
Microalbuminuria (mg/l)	7.7 ± 8.8	14.9 ± 17.9	n.s.
Diabetes duration (years)	19.8 ± 71.5	18.5 ± 9.5	n.s.
Insulin requirement (IU/Kg/die)	0.59 ± 0.4	0.62 ± 0.38	n.s.
Ischemic coronary disease (%)	15	5.7	**<0.001**
Acute myocardial infarction (%)	11	3	**0.03**
Antihypertensive therapy (%)	85	78	n.s.
Statin therapy (%)	64	48	n.s.*
Salicylate therapy (%)	72	44	**<0.001***

Significant statistical analyses are shown in bold

Results are shown as mean value ± SD or percentage (%) as appropriate. Student T test applied. * χ^2 test applied

Remarkably, we demonstrated that patients in treatment with PPIs had an evident and better glycemic control despite being older than PPIs-untreated subjects. This finding may be considered somewhat unexpected and of interest in light of the fact that the achievement of glycemic targets in the elderly is known to be hampered by a number of age-related factors such as increased prevalence of comorbidities (as also observed in our study population), relative inability to tolerate the adverse effects of medication and higher risk of hypoglycemia.

In addition, the percentage of insulin-treated patients, the daily IR and the number of diabetes medications were comparable in the two subgroups, reinforcing the hypothesis that PPIs exert a direct influence on glycemic control in patients with type 2 diabetes. Several patients in our study population were treated with PPIs for drug-induced ulcers prevention, leading to a significantly greater rate of chronic salicylate therapy in PPIs-treated group. As salicylate is known to potentially influence glycemic control, we performed bivariate correlation analyses between salicylate use and HbA1c and FBG showing no association between these variables in our study sample.

Furthermore, we considered as PPIs-treated only subjects taking PPIs chronically for more than 2 years and who were on PPIs treatment when undergoing physical examination and blood sampling; indeed, we also demonstrated that the association between lower HbA1c and PPIs treatment was independent from the PPIs active molecule and their dosage.

Although limited data are available regarding the effects of PPIs on glucose metabolism in humans, our findings are consistent with the few observational and intervention studies published thus far.

Mefford et al. [15] observed that among patients on oral antidiabetic therapy, subjects concomitantly treated with PPIs had lower HbA1c levels than subjects without PPIs therapy.

Accordingly, pantoprazole administration seemed to improve HbA1c, C-peptide and proinsulin levels both in T2D patients and in healthy subjects in a small study recently conducted by Inci et al. [16].

Singh et al. [13] demonstrated in a randomized, double-blinded, placebo-controlled study that patients with type 2 diabetes treated for 12 weeks with pantoprazole in addition to standard antidiabetic therapy had significantly lower HbA1c levels compared to placebo-treated patients. However, Takebayashi et al. [17] failed to demonstrate that combined therapy with PPIs and alogliptin was more effective than alogliptin alone in improving glycemic control during a 3-months study period. Similarly, treatment with esomeprazole did not improve insulin secretion and glycemic control in a population of patients with type 2 diabetes compared with placebo group. However, treatment with PPIs/placebo lasted only 12 weeks, and the study

Table 4 Patients on antidiabetic therapy (without insulin)

	PPIs+ ($n = 153$)	PPIs− ($n = 203$)	p value
Age (years)	68.3 ± 10	63.5 ± 11.7	**<0.001**
Sex (*M*/*F*)	69/84	114/89	**0.02**
BMI (kg/m^2)	30.1 ± 4.9	30.2 ± 5.6	n.s.
SBP (mm/Hg)	131.6 ± 15.8	134.9 ± 16	n.s.
DBP (mm/Hg)	79.6 ± 8.8	83.4 ± 9	**<0.001**
FBG (mg/dl)	121.9 ± 34	137.9 ± 39	**0.001**
HbA_1C (%, mmol/mol)	6.8 ± 0.98, 51 ± 13	7 ± 1.2, 53 ± 10	n.s.
Total cholesterol (mg/dl)	171 ± 40.3	182.2 ± 43.5	**0.02**
HDL cholesterol (mg/dl)	49 ± 14.1	50.1 ± 12.2	n.s.
LDL cholesterol (mg/dl)	97.3 ± 34.8	101.7 ± 36.9	n.s.
Triglycerides (mg/dl)	146.3 ± 81.3	147 ± 121.1	n.s.
AST (IU/l)	21.6 ± 11	22.5 ± 9.8	n.s.
ALT (UI/l)	25 ± 17.7	28.6 ± 15.6	n.s.
γ-GT (IU/l)	44.6 ± 47.5	45.5 ± 42.6	n.s.
Microalbuminuria (mg/l)	18.9 ± 38	17.9 ± 37.3	n.s.
Diabetes duration (years)	9 ± 7	8.5 ± 7.4	n.s.
Ischemic coronary disease (%)	6.7	2.5	**<0.001**
Acute myocardial infarction (%)	12	3	**0.001**
Antihypertensive therapy (%)	83	77	n.s.
Statin therapy (%)	69	62	n.s.*
Salicylate therapy (%)	66	28	**0.001***
Number of antidiabetic agents: (% of patients in treatment)			n.s.°
No antidiabetic drugs (%)	8	5	
1 (%)	53	53	
2 (%)	32	34	
3 (%)	6	7	
4 (%)	1	1	

Significant statistical analyses are shown in bold

Clinical and biochemical characteristics according to the presence (PPIs+) or absence (PPIs−) of chronic PPIs treatment

Results are shown as mean value ±SD or percentage (%) as appropriate. Student T test applied. * χ^2 test applied. ° Bonferroni post hoc-adjusted ANOVA test applied

Table 5 Bivariate correlations between HbA_1C and clinical–biochemical parameters

Parameter	Correlation's coefficient	p value
PPI treatment (yes vs no)	−0.11*	**0.01**
FBG	0.73	**<0.001**
AST	0.11	**0.02**
ALT	0.11	**0.01**
BMI	0.14	**0.006**
Insulin therapy (yes vs no)	0.42*	**<0.001**
Insulin requirement	0.17	**0.03**
Sex (male vs female)	0.1*	**0.02**
Age	0.06	n.s.
Number of antidiabetic drugs (no insulin)	−0.13*	**0.002**
Number of antidiabetic drugs (+insulin)	0.08*	n.s.
Diabetes duration	0.31	**<0.001**
Type of PPI	0.05*	n.s.
Dosage of PPI	0.02*	n.s.
Antihypertensive therapy (%)	*	n.s.
Statin therapy (%)	*	n.s.
Salicylate therapy (%)	*	n.s.

Significant statistical analyses are shown in bold

Pearson's correlation coefficient

*Spearman's correlation coefficient

Table 6 Multivariate linear regression analysis. HbA1c considered as dependent variable

Model		Non-standardized coefficients		Standardized coefficients	*t*	Sig.
		B	Error standard deviation	Beta		
Coefficients[a]						
1	(Constant)	7.258	1.619		4.483	0.000
	Age	−0.015	0.014	−0.107	−1.018	0.311
	Sex (male vs female)	−0.206	0.243	−0.086	−0.848	0.398
	PPIs (yes vs no)	**−0.543**	**0.226**	**−0.236**	**−2.401**	**0.018**
	BMI	0.003	0.019	0.018	0.179	0.859
	Insulin therapy (yes vs no)	1.479	1.167	0.124	1.268	0.208
	Number of antidiabetic drugs	0.115	0.152	0.080	0.754	0.453
	Insulin requirement	0.552	0.303	0.190	1.822	0.072
	Diabetes duration	0.004	0.012	0.034	0.336	0.738

Model	*R*	*R*-squared	Corrected *R*-squared	Estimation error standard deviation
Model summary				
1	0.371[b]	0.138	0.067	1.1173

Significant statistical analyses are shown in bold

[a] Dependent variable: HbA1c

[b] Predictors: (constant), T2D duration, PPI therapy, insulin therapy, insulin requirement, gender, BMI, age, number of antidiabetic drugs

population excluded patients on insulin- and GLP-1-based therapy [18].

Moreover, consistent with our findings, Boj-Carceller et al. [14] found in a population of diabetic patients that those in treatment with PPIs had significantly better glycemic control than subjects without PPIs and this difference was even more evident in patients on insulin and concurrent PPIs therapy.

Since patients on insulin therapy likely represent the ones with the most significant impairment of ß cells insulin secretion, it is possible to hypothesize that the beneficial effects of PPIs on glycemic control in these patients may be due to the role of gastrin on ß cell function.

Indeed, it has been largely proven that chronic PPIs treatment is able to increase circulating levels of gastrin which, in turn, directly promotes insulin secretion and contributes to postprandial hyperglycemia reduction. Moreover, PPIs and the consequent hypergastrinemia improve insulin secretion also indirectly through somatostatin and other antral peptides modulation [19, 20].

Chronic PPIs administration also results in delaying gastric emptying, which in turn may partially account for reduced postprandial glucose levels and increased satiety [10, 11].

A limit of this study is represented by its retrospective design which does not allow to provide a causal nexus between PPIs therapy and improved glucose control; another limit is that although chronic PPIs therapy is expected to induce reactive hypergastrinemia, serum gastrin concentration was not measured in our study population.

Besides this consideration, our study has several strengths: At the bulk of our knowledge, in fact, this is the first study investigating the association between chronic PPIs therapy and glycemic control, evaluated by both FBG and HbA1c, conducted in a large population of patients with type 2 diabetes treated with insulin and/or other antidiabetic agents. Moreover, we performed a scrupulous characterization of our study population in order to detect other possible determinants of metabolic control such as the prevalence of major cardiovascular adverse events and comorbidities, along with concomitant therapies and type/number of antidiabetic agents used for diabetes management.

As it is plausible that PPIs exert their action on glucose control mainly by increasing blood levels of "*GLP-1-like*" hormone gastrin which, in turn, stimulates insulin release, we tested the hypothesis and then confirmed that patients taking more advantage from PPIs therapy with respect to blood glucose control were those with relative insulin deficiency, as insulin-treated subjects. Similarly, we showed the existence of a "synergism" between PPIs and GLP-1-based therapies, leading to improved glycemic control in patients treated concomitantly with both these drugs, and particularly with GLP-1 agonists, likely as a consequence of their matching action on glucose homeostasis.

In conclusion, our data demonstrate that patients with type 2 diabetes treated with PPIs for more than 2 years have significantly better glycemic control compared with diabetic patients not treated with PPI independently from

other confounders. This difference is particularly evident in patients on insulin- or incretin-based therapy. These results suggest a role of PPIs in glucose and insulin homeostasis and may open a new scenario for diabetes therapy.

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Conflict of interest There are no relevant conflicts of interest to disclose.

Ethical standard The study protocol was reviewed and approved by local Ethics Committee, and conducted in conformance with the 1964 Helsinki Declaration.

Human and Animal Rights disclosure All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008.

Informed consent Informed consent was obtained from all patients for being included in the study.

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