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The Difficulty of Diabetic Therapy: An Observational Retrospective Study from Actual Clinical Practice

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Abstract

Aim: The main purpose for a good management of the diabetic disease is to avoid blood glucose swings. This study aims to analyze the diabetic management focusing on iatrogenic hypoglycemia, the therapeutic failure and the Body Mass Index (BMI).

Methods: Diabetic patients were divided into insulin/secretagogue drugs (insulin/SD), Glucagon Like Peptide-1 Receptor Agonist (GLP-1RA) and Dipeptidylpeptidase-4 inhibitors (DPP-4i). An algorithm was created to identify hypoglycemic events, considering fracture discharge, access to emergency for coma or driving mishaps, and Self-Monitoring Blood Glucose. The achievement of glycated hemoglobin (HbA1c) target level (≤ 7%) and BMI target (≤ 25 kg/m^2) were analyzed as well.

Results: 16.23% out of 16,549 patients had at least one hypoglycemic event. Patients taking insulin/SD (94.39%) had a major risk of hypoglycemia (OR=2.01 p<0.001), while the groups with GLP-1 RA (1.87%) and DPP-4i (3.47%) show an OR of 0.59 (p<0.001) and 0.44 (p<0.001), respectively. The therapeutic target of HbA1c was achieved only in patients treated with DPP-4i (6.85% p<0.001). The BMI remained over the target threshold both before and during treatment for all groups but increased only for patients with insulin/SD (from 29.29 to 29.58 kg/m^2). The major decrease in the number of BMI off-target patients was reported for the DPP-4i group (86.2% and 80.1% before and during treatment).

Conclusions: The DPP-4i treatment did not associate with hypoglycemia and allowed HbA1c target achievement. Insulin/SD therapy, in contrast, correlated with an increased risk of hypoglycemic events, weight gain, and failure to achieve hematic target with HbA1c.

Keywords: Diabetes; Pharmacoepidemiology; Real practice; Therapeutic target

Introduction

The main purpose of antidiabetic treatment is to avoid hyperglycemic events that may cause neuropathy, nephropathy, cardiovascular complications, retinopathy and diabetic ulcers [1-4]. Such complications are reduced when the blood glucose level is maintained within the normal range which, however, is quite difficult with some antidiabetic drugs because of "the barrier of hypoglycemia" [5]. An achievement of a lower blood glucose level and a better diabetic management have been described in some clinical studies, such as the DCCT [6], VADT [7] and the UKPDS [8], showing that a tight glycemic control which improves micro-and macrovascular complications, may also cause iatrogenic hypoglycemic events, significantly affecting patient life quality by provoking brain abnormalities, cognitive dysfunction, coma and even death [6-9]. The drugs that better stabilize blood glucose levels are: i) *Acarbose* [10]; ii) *Metformin*; iii) *Pioglitazone* iv) *Dipeptidylpeptidase-4* inhibitors (*DPP-4i*); v) Glucagon Like *Peptide-1* Receptor Agonist (GLP-1 RA) [11,12]. By contrast, drugs mainly causing iatrogenic hypoglycemia are insulin and secretagogue drugs (*sulfonylureas* and *glinides*) [9]. The diabetic management is monitored through the glycated hemoglobin (HbA1c) blood parameter whose target level is set at 7% [13]. The achievement of this value is also correlated to Body Mass Index (BMI): Patient with BMI <25 kg/m^2 present greater rate of therapeutic target achievement with regard to HbA1c [14].

The aim of this study was to retrospectively analyze a 6-year management of antidiabetic therapy in a patient cohort, focusing on iatrogenic hypoglycemia, the therapeutic failure (achievement of the glycated hemoglobin target values), and BMI.

Methods

Data extraction and searches

The study was performed in the Pharmaceutical Service of the Italian Local Health Authority n. 9 (LHA), Treviso district. The local pharmaceutical databases, regarding a cohort of 16,549 diabetic patients, were retrospectively (2008-2013) analyzed: Drug prescriptions, Blood Tests Laboratory (BTL), Self-Monitoring Blood Glucose (SMBG), Access to Emergency (AE) and Hospital.

Discharge Records (HDR). The study starts from 2008 because in this year incretin-based therapies (*DPP-4i and GLP-1 RA*) were introduced into the market.

This was a retrospective observational study, this article does not contain any studies with human participants or animals performed by any of the authors. For this type of studies the approval by the Ethics Committee is not required (GU n. 76 March 31, 2008).

Characterization of the enrolled population

Diabetic patients were enrolled and divided according to the antidiabetic therapy, extracted by ATC (Anatomic Therapeutic Chemicals) codes, and the consequent risk of iatrogenic hypoglycemia into patients treated with: i) Insulin/SD (Insulin and/or Secretagogue Drugs), ii) DPP-4i, iii) GLP-1 RA. Patients simultaneously treated with more than one of these three types of antidiabetic drugs were excluded from the study, as specified in Table 1.

Drug therapy	ATC code	Drugs
Insulin/SD	A10A*, A10BB*, A10BD01, A10BD02, A10BD04, A10BD06, A10BX02	Insulins, all sulfonyureas, fenformin + sulfonyureas, metformin + sulfonylureas, glimepiride + rosiglitazone, glimepiride + pioglitazone + repaglinide
DPP-4i	A10BH*, A10BD07, A10BD08, A10BD11	Sitagliptin, vildagliptin, saxagliptin, linagliptin, sitagliptin + metformin, vildagliptin + metformin, linagliptin + metformin
GLP-1 RA	A10BX04, A10BX07	Exenatide, liraglutide
Excluded	Insulin/SD + DPP-4i + GLP-1 RA	Nil

Table 1: Criteria of subdivision of the enrolled diabetic population according to therapy.

For the population, divided into three groups according with the type of treatment, the mean age of patients, also depending on sex, and the duration of the diabetes disease have been considered. The diabetic duration (years ± Standard Error of the Mean-SEM), in particular has been calculated from the data of diagnosis to the data of enrollment in the study.

Analysis of hypoglycemic event

Hypoglycemic events were identified based on

1. ICD-9 codes (International Classification of Disease-9th Edition) through the databases of the HDR, and of AE applying the algorithm proposed by Ginde et al. [15].
2. Hospital admissions for fracture (through ICD-9) selected on the basis of the main diagnosis, regardless of fracture type. The correlation between hypoglycemic event and fracture should be considered as a proxy.
3. AE for accidents, coma and cognitive dysfunction. The correlation between hypoglycemic event and AE for accidents, coma and cognitive dysfunction should be considered as a proxy.
4. Blood glucose value ≤ 70 mg/dl through SMBG. The SMBG consists of blood glucose level, measured autonomously by the patient, saved and downloaded by the physician, thus ensuring a timely monitoring of the patient (Figure 1).

The presence of one or more of these clinical situations was linked to a hypoglycemic event and so the diabetic patients were considered exposed to hypoglycemia during the treatment.

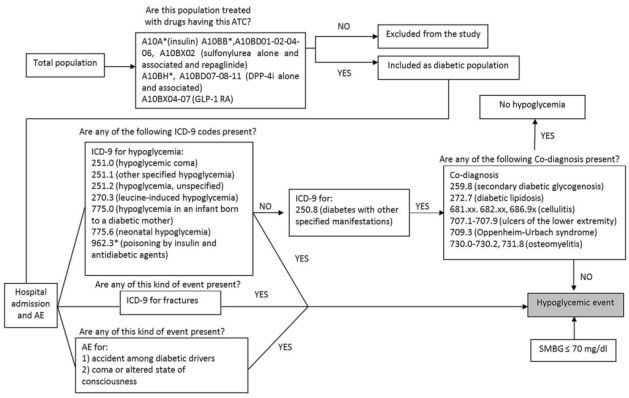

Figure 1: Algorithm for the determination of a possible hypoglycemic event. The illustrated algorithm was used in order to detect any possible hypoglycemic event. ATC: Anatomical Therapeutic Chemical; ICD-9: International Classification of Diseases 9th Edition; AE: Access to Emergency; SMBG: Self-Monitoring Blood Glucose.

Analysis of the therapeutic target's achievement

The effectiveness of the antidiabetic treatment was analyzed considering both the glycated hemoglobin (HbA1c) values and the BMI, only for patients whose values were available. The BTL consists of HbA1c sampling analysis carried out by hospital laboratories. In accordance with the international Guidelines HbA1c values below the threshold of 7% (53 mmol/mol) are associated with good glycemic control and lower exposure to diabetic complications; for this reason, this threshold was considered for achievement of therapeutic target

[13]. In this study patient mean value of HbA1c was analyzed before and during treatment to evaluate changes connected to therapy.

The BMI was considered to evaluate a weight gain and was calculated as weight (kg) divided by height (m) squared. The increase in BMI could be correlated to a poor metabolic control [16] and to an increased risk of cardiovascular events [17]. According to WHO guidelines, 25 kg/m^2 was considered as threshold for BMI, since it represents an overweight situation [18]. Also for this parameter, the mean value before and during the treatment was analyzed.

Statistical analysis

Logistic regression model was performed to analyze categorical variables, including the hypoglycemic event, with sex and type of treatment. Results are presented as Odds Ratios (ORs) with respective 95% CI (Confidence Interval). The effect of therapy was measured by change of HbA1c mean value before and during therapy. The correlation between the average before beginning of therapy and during treatment was calculated for each group. The two different means were compared through t-test with 2-tailed paired data and also the distance of mean value from the therapeutic target threshold was calculated. The difference between mean values of each group was compared using the t-test for unpaired data. Only $p<0.05$ was considered statistically significant. The same analyzes were done with BMI, whose target value was fixed to 25 kg/m^2 beyond which the patient was considered overweight. All statistical tests were performed using Stata 13 software.

Results

Figure 2 shows the percentage of patients selected in this study, according to antidiabetic treatment. The enrolled population was composed of 16,549 patients, the majority treated with insulin/SD (n=15,620, 94.39%), whereas 3.74% (n=619) and 1.87% (n=310) received DPP-4i and GLP-1 RA, respectively.

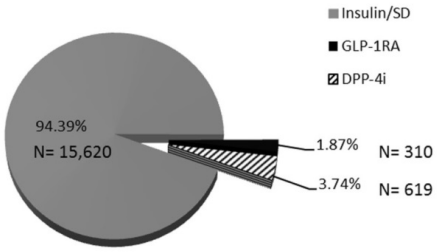

Figure 2: Subdivision of the enrolled diabetic population according to therapy. The diabetic population was divided in relation to antidiabetic therapy (Insulin/SD; *GLP-1* RA and *DPP-4i*) for the period 2008-2013.

The mean age of the population was 68.32 ± 0.11 years and treated men presented a mean age lower than women (66.68 ± 0.13 and 69.97 ± 0.18, respectively). Considering the different treatments, the group treated with GLP-1 RA was the youngest (Table 2).

The mean duration of the diabetic disease, considered where the information was available, did not show a great difference between the three groups. Patients treated with insulin/SD, *GLP-1* RA and DPP-4i had mean diabetic disease durations of 6.64 ± 0.09, 6.00 ± 0.37, and 8.05 ± 0.35 years, respectively, from diagnosis to enrollment in the study.

A hypoglycemic event was more frequent among women than men, affected 17.34% and 15.20% of the two genders, respectively, and the OR of an event linked to low plasma level was 1.17 ($p<0.001$) times higher in women than in men. Patients taking insulin/SD instead are exposed to a statistically significant major risk of hypoglycemia (OR=2.01; $p<0.001$) and represent 16.66% of the studied cohort. The risk of hypoglycemia was calculated also for GLP-1 RA and DPP-4i treatment, each compared to insulin/SD therapy. They presented a lower risk of an event linked to a low blood glucose level compared to insulin/SD therapy (OR=0.59; $p<0.001$ and OR=0.44; $p<0.001$ respectively). The lowest number of hypoglycemic patients was found in the group with *DPP-4i* (8.24%), and in the total population 16.23% of patients had at least one hypoglycemic event (Table 3).

Sex	Drug type			
	Insulin/SD	GLP-1 RA	DPP-4i	TOT
F	70.25 (± 0.75)	58.84 (± 5.18)	67.11 (± 4.23)	69.97 (± 0.18)
M	67.10 (± 0.75)	58.62 (± 4.35)	64.32 (± 3.36)	66.68 (± 0.13)
TOT	68.65 (± 0.11)	58.71 (± 0.55)	65.46 (± 0.45)	68.32 (± 0.11)

Table 2: Mean age and sex of the enrolled diabetic population, divided according to antidiabetic therapy (Insulin/SD; *GLP-1* RA and *DPP-4i*) in the period 2008-2013.

To analyze management of the therapy, the average of HbA1c before and during treatment was examined when data were available (Table 4). Considering the different therapeutic groups before treatment, the mean value was 8.02% (64.16 mmol/mol; 95% CI 7.95-8.08) for patients treated with insulin/SD, 8.38% (68.09 mmol/mol; 95% CI 8.18-8.59) for patients treated with GLP-1 RA, and 7.62% (59.79 mmol/mol; 95% CI 7.51-7.72) for patients treated with DPP-4i. All these values are significantly above the threshold level ($p<0.001$) but are also significantly different from each other ($p<0.01$). During the period of treatment, instead, the mean value was 7.10% (54.10 mmol/mol; 95% CI 7.07-7.14) for patients with insulin/SD, 7.12% (54.32 mmol/mol; 95% CI 6.99-7.25) for patients with GLP-1 RA, and 6.85% (51.37 mmol/mol; 95% CI 6.78-6.92) for patients treated with DPP-4i. For all these groups, a significant decrease following antidiabetic therapy was reported ($p<0.001$). However, the therapeutic target was achieved only in the group with DPP-4i ($p<0.001$); for the other groups the mean HbA1c levels during treatment were, instead, above threshold level ($p<0.001$ for insulin/SD treated patients; $p>0.05$ for GLP-1 RA). Between these last two groups, in fact, no significant difference emerged ($p>0.05$); on the other hand, both of these groups were significantly higher than the DPP-4i group ($p<0.001$).

The observed BMI, calculated for available data, always significantly exceeded the overweight target threshold (25 kg/m^2) ($p<0.001$) (Table 5). In particular, before treatment mean BMI value was 29.29 kg/m^2 (95% CI 29.13-29.44) for patients treated with insulin/SD, 34.96 kg/m^2 (95% CI 34.02-35.89) for patients treated with *GLP-1* RA, and 29.74 kg/m^2 (95% CI 29.14-30.33) for patients treated with *DPP-4i*. These values differed from each other ($p<0.001$) except for the groups insulin/SD vs *DPP-4i* ($p>0.05$). Therapy in every case reduced BMI

mean value (p<0.001) except for the group treated with insulin/SD, where the level increased from 29.29 kg/m^2 to 29.58 kg/m^2 (p<0.001). For the other two groups the mean BMI values during treatment were 34.07 kg/m^2 (95% CI 33.09-35.03) for GLP-1 RA and 28.99 kg/m^2 (95% CI 28.38-29.59) for DPP-4i. Moreover, these values differed significantly from each other (p<0.05).

DPP-4i treatment also reduced the number of off-target patients from 86.2% to 80.1% before and during treatment, respectively and in the insulin/SD treated group 83.1% and 82.8% of patients were off-target both before and during therapy, respectively (Figure 3). Patients treated with GLP-1 RA, instead, showed no difference in the number of off-target subjects from before to during therapy but they had the highest reduction in mean BMI value (-0.89 from before to during treatment).

Hypoglycemic event		**OR**	**Std. Err.**	**z**	**P>|z|**	**[95% Conf. Interval]**	
Sex	**F vs. M**	1.17	0.05	3.72	p<0.001	1.08	1.27
Therapy with hypoglycemic risk	Insulin and/or SD vs. GLP-1 RA or DPP-4i	2.01	0.23	6.00	p < 0,001	1.60	2.52
	GLP-1 RA vs. Insulin and/or SD	0.59	0.11	-2.79	0.005	0.41	0.85
	DPP-4i vs. Insulin and/or SD	0.44	0.07	-5.42	p < 0,001	0.33	0.60

Table 3: Risk (Odds Ratio) of hypoglycemia based on gender and on antidiabetic therapy, i.e., insulin/SD vs. the other type of treatment (GLP-1 RA and DPP-4i), insulin/SD vs. GLP- RA and insulin/SD vs. DPP-4i.

HbA1c		**N. obs**	**Mean % (mmol/mol)**	**Std. Err.**	**Std. Dev.**	**[95% Conf. Interval]**		**Δ during-before**
Insulin/SD	Before treatment	3601	8.02 (64.16)◊	0.03	2.04	7.95	8.08	- 0.92
	During treatment	3601	7.10 (54.10)*◊	0.19	1.14	7.07	7.14	
GLP-1 RA	Before treatment	208	8.38 (68.09)◊	0.10	1.48	8.18	8.59	- 1.26
	During treatment	208	7.12 (54.32)*	0.07	0.95	6.99	7.25	
DPP-4i	Before treatment	360	7.62 (59.79)◊	0.05	1.04	7.51	7.72	- 0.77
	During treatment	360	6.85 (51.37)*◊	0.03	0.65	6.78	6.92	

Table 4: Average glycated hemoglobin level before and during treatment.

BMI		**N. obs**	**Mean % (kg/m^2)**	**Std. Err.**	**Std. Dev.**	**[95% Conf. Interval]**		**Δ during-before**
Insulin/SD	Before treatment	4355	29.29◊	0.78	5.16	29.13	29.44	0.29
	During treatment	3601	29.58*◊	0.79	5.20	29.43	29.73	
GLP-1 RA	Before treatment	203	34.96◊	0.47	6.78	34.02	35.89	- 0.89
	During treatment	203	34.07*◊	0.49	6.99	33.09	35.03	
DPP-4i	Before treatment	312	29.74◊	0.30	5.35	29.14	30.33	- 0.75
	During treatment	312	28.99*◊	0.31	5.42	28.38	29.59	

Table 5: BMI before and during treatment.

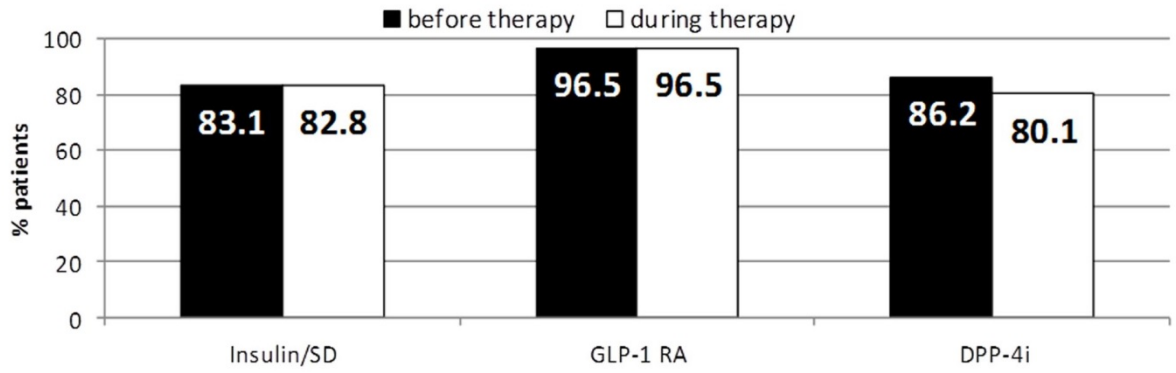

Figure 3: Evaluation of BMI before and during antidiabetic therapy. BMI values were calculated before and during therapy with insulin/SD, GLP-1 RA and DPP-4i. The number of patients (%) with a mean BMI over the target threshold (25 kg/m^2) is reported for each therapeutic group separately.

Discussion

In this study, hypoglycemic events were identified, as proxy, according to an algorithm, which included also fracture diagnosis extracted from HDR databases. Some reasons for fracture hospitalization would be treatment with pioglitazone, lack of vitamin D, and bone density, which is lower in type 1 diabetic patients [19]. Beside fractures, AE for accidents were considered in the algorithm, as well. The choice of including them comes from the consideration that hypoglycemia might be a primary cause of them. Even if not all accidents by diabetic patients are linked to a drop in blood glucose levels, a recent study by Cox et al. [20] shows that hypoglycemia is a common and unique risk factor for driving mishaps, which is also higher among type 1-diabetic patients treated with insulin.

Considering the linkage of hypoglycemic events and therapy, in particular, our results showed that insulin/SD treatment was correlated with risk of a hypoglycemic event two-fold higher than the other types of treatment in exam (*DPP-4i and GLP-1 RA*) [21]. In particular, women appeared to be at higher risk as found by Giorda et al. in the Hypos-1 study [22]. In the present study the considered groups are different and patients treated with DPP-4i have a course of disease two years longer than those with GLP-1 RA. The probability of hypoglycemia with insulin and SD all together was two-fold higher than the risk for patients treated with *DPP-4i and GLP-1 RA*. Thus, both DPP-4i and GLP-1 RA provide a better glycemic control than therapy with insulin/SD [23]. Between treatment with *DPP-4i* and *GLP-1* RA the lower risk of hypoglycemia was for patients with the first type of therapy.

The findings in this study indicate that insulin/SD increases the risk of hypoglycemia, but also keeps the diabetic patients above the HbA1c target threshold of 7%, as reported by Bryant et al. [24]. The present analysis did not consider the type of diabetes, but only the therapy because its aim was to assess management of the hypoglycemia and achievement of HbA1c target level during therapy. Regardless of the type of therapy, about half of the patients were off target (data not shown). The group of patients in therapy with GLP-1 RA was not below the target threshold for HbA1c, in contrast to other studies such as that of Pratley et al. [25], in which exenatide and liraglutide improved more the glycemic control if compared to DPP-4is. In accord with Sanjay et al. [26], it has revealed that the only group that achieved the therapeutic target was treated with *DPP-4i* but these patients presented also a significantly lower starting HbA1c than those of the other two groups. Contrarily patients treated with GLP-1 RA had the highest HbA1c mean value before treatment but they did have the best HbA1c reduction, probably because patients with a higher initial HbA1c seem to have a greater glycemic response to therapy [26-28]. Incretin-based therapy in general and GLP-1 RA in particular, are often used for obese patients, because their mechanism of action delays gastric emptying, suppresses appetite, and improves satiety. All these factors result in weight loss, and are helpful in motivating diabetic patients [29]. In the present study the number of patients over the BMI target threshold decreased only with *DPP-4i* therapy but the group treated with *GLP-1* RA has the greatest weight loss. Insulin, instead, produced a weight gain that could be a barrier to glycemic control [30]. In fact, in the present study the BMI before and during treatment with insulin/SD increased while the number of patients with a BMI value off target remains the same.

In conclusion the management of diabetes is not always simple despite the many drugs developed to keep blood glucose and HbA1c values within a defined range to avoid hypoglycemia, hyperglycemia and their clinical consequences. The diabetes is also a very complex disease and it is not so easy to keep patients on target avoiding a hypoglycemic event. This retrospective study on a very large diabetic cohort shows that not all these therapies (insulin/SD and *GLP-1 RA*) are effective in reducing HbA1c blood level; in fact, only *DPP-4i* allowed patients to reach the hematic therapeutic goal. Furthermore, *DPP-4i* treatment was not associated with hypoglycemia, whereas insulin/SD therapy correlated with an increased risk of hypoglycemic events that included also hospitalizations.

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Competing Interests

All authors have completed the Unified Competing Interest form at http://www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare: no support from any organization for the submitted work; no financial relationship with any organizations that might have an interest in the submitted work in the previous 3 years; no other relationship or activities that could appear to have influenced the submitted work.

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