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ORIGINAL ARTICLE

Adjustment of insulin doses when switching from glargine 100 U/ml or detemir to degludec: an observational study

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Abstract

Background Degludec is a long-acting insulin with a longer duration of action and a greater day-to-day reproducibility of absorption in comparison with previous long-acting insulin formulations. The aim is the definition of the change in insulin needs in patients switching from detemir/glargine to degludec in real-life conditions.

Methods In this retrospective cohort observational study, all outpatients with either type 1 or type 2 diabetes, starting therapy with degludec insulin—after a prior treatment with either detemir or glargine insulin for at least 6 months—were included.

Results The analysis was performed on 266 patients, 172 and 96 with type 1 and type 2 diabetes, respectively. The equations describing the relationship between baseline and follow-up doses of basal insulin (6 months) were $Y = 3.39 + 0.78X$ and $Y = 0.44 + 0.69X$, in patients receiving detemir/glargine either once or twice daily, respectively (Y = degludec dose at 6 months and X = basal insulin dose at switch). The corresponding equations for prandial insulin doses were $y = 1.83 + 0.83*x$ and $y = 2.85 + 0.80*x$ for those on pre-switch once or twice-daily basal insulin, respectively. In type 2 diabetes, the switch was associated with a reduction of basal insulin doses only in those with a prior twice-daily treatment with basal insulin. The reduction of prandial insulin reached statistical significance only in patients previously treated with basal insulin once daily.

Conclusions The present results provide a suggestion for a simple method for the adjustment of basal and prandial insulin doses in type 1 diabetic patients, switching from glargine or detemir to degludec.

Keywords Type 1 diabetes · Type 2 diabetes · Insulin · Degludec · Basal insulin · Prandial insulin

Introduction

Degludec is a long-acting insulin used in the treatment of diabetes. In comparison with previously available long-acting insulin formulations (human NPH insulin, glargine, and detemir), degludec has a longer duration of action and a greater day-to-day reproducibility of absorption after subcutaneous injection [1–3]. As a consequence, the use of degludec insulin is associated with a lower risk of overall and nocturnal hypoglycemia, both in type 1 and type 2 diabetes [4–6]. These advantages may prompt physicians to switch from glargine or detemir to degludec in some patients, to reduce hypoglycemic risk.

In randomized clinical trials, when compared to either glargine (in the 100 U/ml formulation) or detemir, after an appropriate titration, the use of degludec is associated with a significant reduction of insulin doses, both for long-acting (basal) and short-acting (prandial) insulin [5–7]. As a consequence, it could be necessary to reduce basal and prandial insulin doses when switching from glargine or detemir to degludec. In patients with type 1 diabetes, the use of degludec, in comparison with glargine, is associated with a 12–13% reduction of both basal and prandial daily insulin doses [6]. The reduction in basal insulin doses has been reported to be greater in patients who were previously on two injections of basal (detemir or glargine) insulin, in comparison with those who were previously treated with long-acting insulin once daily [8–11]. A similar difference was observed in trials on type 2 diabetes on basal-only insulin regimens, whereas no significant reduction of insulin doses has been associated with degludec in patients with type 2 diabetes on basal-bolus therapy [6].

Although suggestive, data obtained in randomized clinical trials cannot be automatically transferred to routine clinical practice. In particular, the relatively aggressive dose

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titration algorithms for basal insulin used in clinical trials, with frequent patient contacts and accurate supervision, are not easily applied in real-world conditions; in addition, patients enrolled in clinical trials are not totally representative of the population of patients receiving basal insulin in clinical practice. For those reasons, observational data can add further information on modifications of insulin doses in the switch from glargine or detemir to degludec. A meta-analysis of observational studies on Japanese patients with type 1 or 2 diabetes switching from glargine or detemir to degludec reported a reduction of 9 and 5.5% of basal insulin doses in patients with type 1 and type 2 diabetes, respectively [12]. In a small 3-month prospective observational study performed in European patients with type 1 diabetes, the switch from twice-daily glargine or detemir to once daily degludec was associated with a 24% reduction of basal insulin dose, together with a 10% reduction of prandial insulin dose [13].

In the present study, we retrospectively assessed the variation of insulin doses 6 months after the switch from glargine or detemir to degludec. The aim is the definition of the change in insulin needs in different subgroups of patients (type 1 and type 2 diabetes; prior therapy with once- or twice-daily basal insulin; prior therapy with detemir or glargine) in real-life conditions, to gather information useful for the adjustment of insulin doses at the moment of the switch.

Subjects, materials, and methods

The study was designed as a retrospective, single-center, cohort observational study. All outpatients with either type 1 or type 2 diabetes, who started therapy with degludec insulin between October 1st, 2014, and November 1st, 2016, after a prior treatment with either detemir or glargine insulin for at least 6 months, were included in the study, provided that they gave their written informed consent. Patients with HbA1c greater than 80 mmol/mol or ketoacidosis at the moment of the switch from detemir/glargine to degludec were excluded, as well as those with critical illness and those needing corticosteroid therapy. The analysis was performed on all patients for whom a follow-up determination of HbA1c and information on insulin doses were available from clinical records 6 (± 2) months after the switch.

According to the local standards, basal insulin is administered at bedtime if once daily, whereas the second injection of basal insulin, when needed, is added before lunch. For degludec, the standard is once daily at bedtime. It is possible that a different timing was used in some patients, but this information is not available from clinical report forms.

Information on demographic and clinical characteristics at the beginning of degludec therapy, together with data on HbA1c and insulin doses at switch and at follow-up, was collected from clinical records. Episodes of severe hypoglycemia (i.e., requiring third-party assistance) during the 6 months preceding the switch, and in the following, 6 months were also collected from clinical records.

Data are reported as mean ± SD, or as median [quartiles], depending on their distribution. Comparisons at different timepoints were performed using Levene's or Wilcoxon's test. Correlation analyses were performed applying Spearman's method. Multivariate analyses were performed using stepwise linear regression models. All analyses were performed on SPSS 24.

The study was approved by the local ethical board.

Results

Characteristics of the sample

The analysis was performed on a sample of 266 patients, 172 and 94 with type 1 and type 2 diabetes, respectively. The main demographic and clinical characteristics of patients at the moment of the switch from either detemir or glargine to degludec insulin is summarized in Table 1. Among patients with type 1 diabetes, 91 (53%) and 81 (47%) had a prior treatment with detemir or glargine, respectively—all in combination with prandial therapy with a rapid-acting analogue (lispro, aspart, or glulisine). Among patients with type 2 diabetes, 59 (63%) and 35 (37%) had been previously treated with detemir or glargine, respectively. Basal insulin was associated with prandial insulin in 85 (80%) patients; in addition, 54 (57.4%) patients were treated with metformin, 5 with DPP4i, 6 with SU, 2 with acarbose, 1 with pioglitazone and 1 with liraglutide.

Among patients with type 1 diabetes, the majority of those treated with detemir received two daily injections of basal insulin (59 and 32 with two and one injection), whereas the majority of those on glargine insulin received basal insulin once daily (15 and 66 with two and one injections). Among patients with type 2 diabetes, only 29 and 4 on detemir and glargine, respectively, were treated with basal insulin twice daily. Six months after the switch to degludec, all patients were treated with basal insulin once daily. After 6 months from the switch, Body Mass Index was not significantly different from baseline (25.1 ± 3.8 and 32.6 ± 7.4 kg/m^2 in patients with type 1 and type 2 diabetes, respectively).

Type 1 diabetes

After 6 months from the switch, HbA1c showed a significant reduction from baseline (58.6 ± 9.6 versus 62.0 ± 9.4 mmol/mol; $p < 0.001$). In addition, a significant reduction of both basal and prandial insulin doses was observed (18 [13; 23]

Table 1 Main demographic and clinical characteristics of included patients

	Type 2 diabetes			*p*	Type 1 diabetes			*p*
	All ($n=94$)	1 Injection ($n=61$)	2 Injections ($n=33$)		All ($n=172$)	1 injection ($n=98$)	2 injections ($n=74$)	
Age (years)	46.3 ± 14.9	47.9 ± 16.7	44.1 ± 11.8	0.51	70.3 ± 8.7	70.5 ± 8.8	70 ± 8.6	0.63
Women (*n*, %)	88 (51.2)	50 (51.0)	34 (45.9)	0.51	47 (50.0)	28 (59.6)	19 (40.4)	0.28
Body Mass Index (Kg/m^2)	25 ± 3.8	25.0 ± 3.6	25.1 ± 4.0	0.86	32.4 ± 7.6	32.3 ± 7.3	32.6 ± 8.3	0.65
Duration of diabetes (years)	20.8 ± 12.3	19 ± 12.5	23.1 ± 11.8	0.73	21.2 ± 10.4	21.6 ± 11.2	20.5 ± 9.1	0.22
HbA1c (%)	62.0 ± 9.4	61.3 ± 8.9	62.9 ± 10.1	0.14	65.3 ± 10.1	66.2 ± 10.5	63.6 ± 8.7	0.19
Creatinine (mg/dl)	0.77 ± 0.18	0.78 ± 0.17	0.76 ± 0.18	0.90	1.12 ± 0.52	1.17 ± 0.51	1.06 ± 0.53	0.24
Total cholesterol (mg/dl)	178.8 ± 31.7	180.5 ± 32.0	176.6 ± 31.2	0.82	171.4 ± 33.7	168.3 ± 33.0	176.3 ± 34.7	0.98
HDL-cholesterol (mg/dl)	60.9 ± 15.4	61.7 ± 16.2	59.9 ± 14.4	0.65	49.1 ± 12.9	49.6 ± 12.5	48.4 ± 13.7	0.74
Triglycerides (mg/dl)	86.6 ± 43.8	82.6 ± 34.9	91.9 ± 53.0	0.018	143.7 ± 65.5	143.8 ± 70.0	143.5 ± 57.9	0.97
LDL-cholesterol (mg/dl)	100.7 ± 26.1	102.3 ± 25.9	98.6 ± 26.4	0.53	94.4 ± 28.0	91.7 ± 26.5	99.2 ± 30.3	0.31
Pharmacological treatments								
Insulin detemir (*n*. %)	91 (52.9)	32 (32.7)	59 (79.0)	< 0.001	59 (62.8)	30 (49.2)	29 (87.9)	< 0.001
Insulin glargine (*n*. %)	81 (47.1)	66 (67.3)	15 (20.3)	< 0.001	35 (37.2)	31 (50.8)	4 (12.1)	< 0.001
Prandial insulin dose (IU/die)	26.3 ± 12.8	27.1 ± 13.5	25.3 ± 12.0	0.97	37.2 ± 25.2	37.5 ± 24.0	36.8 ± 27.7	0.70
Basal insulin dose (IU/die)	22.4 ± 10.5	18.2 ± 9.1	27.9 ± 9.8	0.95	33.2 ± 21.4	24.7 ± 13.3	48.9 ± 24.7	< 0.001
Metformin (*n*, %)	32 (18.6)	17 (52.8)	15 (47.3)	0.89	54 (57.4)	43 (80.2)	11 (20.0)	< 0.001
Acarbose(*n*. %)	–	–		–	2 (2.1)	2 (3.3)	0 (0.0)	0.29
Sulfonylureas (*n*. %)					6 (6.4)	3 (4.9)	3 (9.1)	0.43
Dypeptidyl Peptidase-4 inhibitors (*n*. %)	–	–	–	–	5 (5.3)	4 (6.6)	1 (3.0)	0.47
Glucagon-like peptide-1 analogues (*n*. %)	–	–	–	–	1 (1.1)	1 (1.6)	0 (0.0)	0.46
Medical history (*n*. %)								
Active smokers	33 (19.2)	18 (10.5)	15 (8.7)	0.85	4 (4.3)	2 (3.3)	2 (6.1)	0.24
Ex-smokers	31 (18)	19 (11)	12 (7.0)	0.85	30 (31.9)	23 (37.7)	7 (21.2)	0.73
Hypertension	51 (29.7)	32 (18.6)	19 (11)	0.32	84 (89.4)	55 (90.2)	29 (89.4)	0.88
Ischemic heart disease	8 (4.7)	5 (2.9)	3 (1.7)	0.75	35 (37.2)	25 (41.0)	10 (30.3)	0.43
Stroke	3 (1.7)	1 (0.6)	2 (1.2)	0.40	12 (12.8)	9 (14.8)	3 (9.1)	0.37
Renal impairment (eGFR < 90 ml/min)	25 (14.5)	18 (10.5)	7 (4.1)	0.10	71 (75.5)	46 (75.4)	25 (75.8)	0.75
Microalbuminuria	21 (12.3)	12 (7.0)	9 (5.3)	0.97	42 (44.7)	30 (50)	12 (36.4)	0.21
Diabetic retinopathy	37 (21.5)	19 (11.0)	18 (10.5)	0.43	45 (47.9)	29 (47.5)	16 (48.5)	0.56
Diabetic neuropathy	27 (15.7)	17 (10.0)	10 (5.8)	0.49	38 (40.4)	29 (47.5)	9 (27.3)	0.060
Foot ulcers	4 (2.3)	2 (1.2)	2 (1.2)	0.78	6 (6.4)	6 (9.8)	0 (0.0)	0.33

Table 1 (continued)

	Type 2 diabetes			*p*	Type 1 diabetes			*p*
	All (*n* = 94)	1 Injection (*n* = 61)	2 Injections (*n* = 33)		All (*n* = 172)	1 injection (*n* = 98)	2 injections (*n* = 74)	
Previous hypoglycemic episodes (*n*. %)								
Severe hypoglycemia	6 (3.5)	5 (3.0)	1 (0.6)	0.18	3 (3.2)	1 (1.6)	2 (6.1)	0.24
Nocturnal hypoglycemia	153 (89)	83 (48)	70 (41)	0.04	60 (63.8)	32 (52.5)	28 (84.8)	0.002

Table 2 Variation in insulin daily doses in subgroups with 1 or 2 basal insulin injection/die at the switch

Group	Prandial doses				Basal doses			
	At the switch	At 6 months	Difference % [95%, CI]	*p*	At the switch	At 6 months	Difference % [95%, CI]	*p*
DM 1								
All	23 [17; 32]	22 [16; 30]	− 7 [− 19; 0]	< 0.001	22 [14; 29]	18 [13, 23]	− 13 [− 27, 0]	< 0.001
1 Inj	25 [18; 34]	23 [16; 30]	− 0 [− 12; 7]	< 0.001	16 [11, 25]	16 [12, 22]	− 8 [− 20; 0]	0.110
2 Inj	22 [16; 30]	20 [16, 28]	− 5 [− 17; 4]	0.006	28 [22; 33]	19 [14, 23]	− 28 [− 38; − 20]	< 0.001
DM 2								
All	33 [21; 51]	30 [20; 45]	− 5 [− 17; 1]	0.006	28 [18; 45]	24 [16; 42]	− 7 [− 23,11]	0.006
1 Inj	37 [20; 52]	31 [21; 45]	− 5 [− 18; 4]	0.055	21 [14; 34]	21 [15; 34]	0 [− 12; 17]	0.550
2 Inj	30 [20; 51]	26 [17; 46]	− 6 [− 16; 0]	0.042	45 [26; 68]	35 [18; 57]	− 20 [− 36; − 8]	< 0.001

DM diabetes mellitus, *Inj*. injection

Table 3 Variation in insulin daily doses in subgroups pre-treated with detemir or glargine at the switch

Group	Prandial doses				Basal doses			
	At the switch	At 6 months	Difference %	*p*	At the switch	At 6 months	Difference %	*p*
DM 1								
All	23 [17; 32]	22 [16; 30]	− 7 [− 19, 0]	< 0.001	22 [14; 29]	18 [13, 23]	− 13 [− 27, 0]	< 0.001
Detemir	22 [17; 34]	20 [16; 30]	− 7 [− 22; − 0]	< 0.001	23 [14; 32]	16 [13, 22]	− 22 [− 34; − 7]	< 0.001
Glargine	24 [18; 32]	23 [16; 30]	− 5 [− 15; 0]	0.003	22 [13, 27]	19 [13, 24]	− 7 [− 16; 1]	< 0.001
DM 2								
All	33 [21; 51]	30[20; 45]	− 5 [− 17,1]	0.006	28 [18; 45]	24 [16; 42]	− 7 [− 23; 11]	0.006
Detemir	37 [22; 60]	29 [17; 44]	− 6 [− 18; 0]	< 0.001	34 [18; 50]	24 [16; 40]	− 11 [− 29; 0]	< 0.001
Glargine	31 [18; 40]	30 [22; 49]	− 5 [− 14; 9]	0.96	22 [14; 38]	24 [16; 43]	+ 4 [− 10, 25]	0.003

DM diabetes mellitus, *Inj.* injection

versus 22 [14; 29] UI/die; 22 [16; 30] versus 23 [17; 32] UI/die; both $p < 0.001$). The initial dose of degludec prescribed was 20 [13; 29] UI/die. The switch to degludec was associated with a reduction of basal insulin doses only in patients with a prior twice-daily treatment, but not in those previously receiving basal insulin once daily; furthermore, the reduction of basal insulin doses was significant in patients previously treated with detemir, but not with glargine. A significant reduction of prandial insulin was observed in patients previously treated with basal insulin once or twice daily, irrespective of the type of prior insulin (Tables 2, 3). Episodes of severe hypoglycemia (one per patient) were recorded in 3 and 2 subjects before and after the switch, respectively.

In type 1 diabetes, percent reduction of basal insulin doses showed a significant direct correlation with baseline basal doses ($r = 0.51$, $p < 0.001$) and duration of diabetes ($r = 0.30$, $p < 0.001$), whereas percent reduction of prandial insulin showed a significant direct correlation with baseline prandial doses ($r = 0.21$, $p = 0.005$) and age ($r = 0.24$,

$p=0.002$), and an inverse correlation with eGFR ($r=-0.15$, $p=0.049$). No significant correlation was detected with baseline HbA1c (data not shown). A linear regression model was used for multivariate analysis, with percent variation of basal insulin dose as dependent variable, including duration of diabetes, basal insulin dose, number of basal insulin daily injections at enrolment, and type of basal insulin (detemir or glargine) as putative determinants. The variation of basal insulin doses was significantly correlated with duration of diabetes ($\beta=-0.126$; $p=0.50$), number of injections ($\beta=-0.369$; $p<0.001$), and doses of basal insulin before switch ($\beta=-0.344$ $p<0.001$), but not prior type of basal insulin. A similar model was used for the variation of prandial insulin doses, adjusting for duration of diabetes, baseline prandial insulin doses, number of basal insulin daily injections at enrolment, type of basal insulin (detemir or glargine), age, and eGFR. The percent variation of prandial insulin doses showed a significant correlation only with the number of daily basal insulin injections before the switch ($\beta=-0.57$; $p<0.001$).

In a linear regression model, when analyzing separately patients with type 1 diabetes receiving detemir/glargine either once or twice daily, the equations describing the relationship between baseline and follow-up doses of basal insulin were $Y=3.39+0.78X$ and $Y=0.44+0.69X$, respectively, where $Y=$degludec dose at 6 months and $X=$basal insulin dose at switch (Fig. 1a). The corresponding equations for prandial insulin doses were $y=1.83+0.83*x$ and $y=2.85+0.80*x$ for those on pre-switch once or twice-daily basal insulin, respectively (Fig. 1b).

Type 2 diabetes

In patients with type 2 diabetes, 6-month HbA1c was significantly lower than baseline (58.7 ± 9.7 versus 65.3 ± 10.1, $p<0.001$). Both basal and prandial insulin doses showed a significant reduction during the 6-month follow-up (24 [16; 42] versus 28 [18; 45] UI/die difference, 30 [20; 45] versus 33 [21; 51] UI/die, respectively, both $p=0.006$). The initial dose of degludec prescribed was 28 [16; 46] UI/die. The switch to degludec was associated with a reduction of basal insulin doses only in those with a prior twice-daily treatment with basal insulin. The reduction of prandial insulin reached statistical significance only in patients previously treated with basal insulin once daily (Tables 2, 3). One patient has experienced one episode of severe hypoglycemia in the 6 months before the switch, and another one reported one episode during the 6-month follow-up after the switch. During the 6-month follow-up after the switch, treatment with sulfonylurea (gliclazide ER 30 mg) was withdrawn in one patient; no other variations in non-insulin therapy resulted from clinical records.

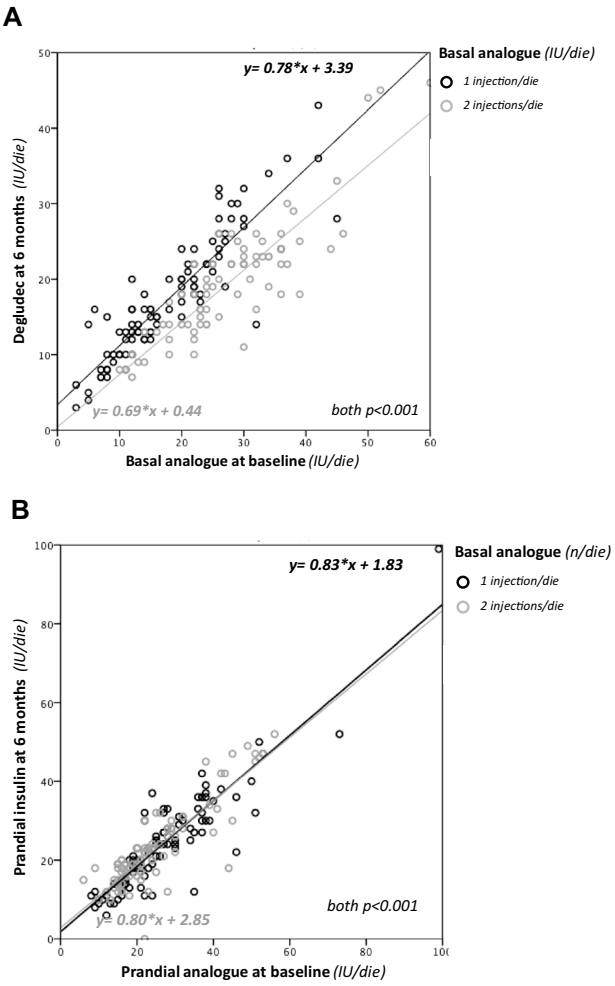

Fig. 1 **a** Describes the relationship between baseline and follow-up doses of basal insulin in type 1 diabetic patients receiving detemir/glargine either once or twice daily; **b** describes the relationship between baseline and follow-up doses of prandial insulin in type 1 diabetic patients receiving detemir/glargine either once or twice daily

At univariate analysis, in patients with type 2 diabetes, the percent reduction of basal insulin doses showed a significant direct correlation with baseline doses ($r=0.36$ $p<0.001$), whereas prandial insulin showed a significant direct correlation with diabetes duration ($r=0.27$ $p=0.01$). No significant correlation was detected with baseline HbA1c (data not shown). At multivariate analysis, using the same models specified above, the percent variation of basal insulin doses maintained a significant correlation with prior doses of basal insulin and with diabetes duration ($\beta=-0.28$ [$p=0.026$] and -0.21 [$p=0.044$], respectively). The variation of prandial insulin doses was significantly correlated with the number of daily basal insulin injections and with diabetes duration ($\beta=-0.29$ [$p=0.006$] and -0.21 [$p=0.039$], respectively).

Discussion

In parallel–series randomized clinical trials comparing degludec with either glargine or detemir, degludec doses at endpoint are usually lower than those of comparators, both in type 1 [8–10, 14, 15] and type 2 [6, 16, 17] diabetes. The reduction of basal insulin doses with degludec in clinical trials appears to be greater in patients previously receiving two daily injections of basal insulin [4, 8]. In several trials, degludec use was also associated with a lower dose of prandial insulin than comparators [6, 7, 9, 10, 14, 15], although some studies failed to detect this difference [8]. In a 2-week crossover trial on a small sample of patients with type 1 diabetes, degludec was associated with a lower dose of prandial, but not basal, insulin when compared to glargine [18].

Randomized clinical trials are the ideal tool for exploring the efficacy and safety of any new treatment, but they do not necessarily provide an accurate picture of real-life conditions. With respect to the aim of this study, i.e., changes in insulin doses when switching from glargine or detemir to degludec, randomized trials could produce some biases. In fact, titration schedules for basal insulin in those studies follow algorithms based on morning fasting glucose, which may be rather different from those used for adjustment of insulin doses in routine clinical practice [19, 20]. Notably, the kinetics of degludec is considerably different from those of both glargine and detemir, producing, if they are all administered at bedtime, higher circulating insulin concentrations in the afternoon [21, 22]. As a consequence, it is conceivable that clinicians titrate degludec considering pre-dinner glucose along with morning fasting glycemia. In addition, patients enrolled in clinical trials are not necessarily representative of those receiving basal insulin in clinical practice. For all those reasons, observational studies can add some information on dose adjustments when switching from glargine or detemir to degludec.

There are a small number of prospective observational studies assessing the change in basal and prandial insulin needs in patients switching from other basal insulin analogues to degludec. In patients with type 1 diabetes, a significant reduction has been reported for prandial insulin doses, whereas a reduction of basal insulin doses occurred only in patients previously treated with two daily injections of basal insulin [23, 24]; conversely, no significant variation of either prandial or basal insulin doses was observed in type 2 diabetes [23].

Prospective observational studies have the advantage of collecting pre-defined data in a controlled setting. On the other hand, prospective observations tend to alter the spontaneous behaviors of both clinicians and patients. Therefore, retrospective observational studies, despite the limitation related to the possible incompleteness of data, may be closer to actual clinical practice. To our knowledge, only one such retrospective study exploring the change of insulin doses after switch to degludec is available so far. It is a survey on 360 patients with type 1 diabetes, reporting a reduction of basal insulin dose in those switching from detemir to degludec, but not in patients switching from glargine to degludec [25]. Due to its shorter duration of action, detemir is used twice daily in type 1 diabetes more often than glargine [26, 27]; unfortunately, in the retrospective study reported above, no separate analysis was performed on patients previously treated with basal insulin either once or twice daily. This point is relevant, considering that, both in randomized trials and prospective observational studies, the reduction of basal insulin doses is more evident in patients previously treated with twice-daily basal insulin [28].

The present study shows a significant reduction of basal insulin when switching from twice-daily glargine or detemir to once daily degludec in type 1 diabetes, whereas only a nonsignificant trend was observed in those switching from once daily basal insulin. These results confirm those reported in clinical trials and prospective observations [8–10, 13–15, 23, 24, 28]. In addition, a reduction of prandial insulin doses was observed after the switch, irrespective of the number of previous daily basal insulin injections [13, 18, 23]. Notably, the reduction of insulin doses occurred together with an improvement of glycemic control, as reported by some previous studies [13, 23, 28].

The data collected in this retrospective observation were used for developing simple equations, to calculate the needed adjustment of insulin doses when switching from glargine or detemir to degludec in type 1 diabetes. As a rule of the thumb, in patients previously treated with once daily basal insulin, basal insulin doses should be reduced by 20%, adding 3 UI; in patients previously on twice-daily basal insulin, degludec dose should be about 30% lower than that of prior basal insulin. In addition, a 20% reduction of prandial insulin doses should be recommended, irrespective of the number of daily basal insulin injections before the switch.

The variations of both basal and prandial insulin doses in type 2 diabetes appear to be consistent with those observed in patients with type 1 diabetes. In the present sample, the large majority of patients with type 2 diabetes switching to degludec was on basal-bolus therapy; therefore, this study cannot provide reliable information on dose adjustments in patients on basal insulin only.

The small size of the sample enrolled in the present study warrants caution in the interpretation of results. In addition, this retrospective survey was performed in a single specialist clinic for diabetes care, limiting the generalizability of results. In fact, type 1 diabetic patients

switching from other basal insulins to degludec are not representative of all those with type 1 diabetes. Furthermore, the specific clinical context, in which patients were regularly visited by trained specialists, could have affected dose titration. The proposed algorithm for dose titration in the switch should, therefore, be validated through specifically designed studies. It should also be recognized that the available sample of patients with type 2 diabetes is very small, so that those specific results should be intended as preliminary. Another limitation is represented by the lack of data on mean fasting glucose, which is impossible to standardize in retrospective studies. The retrospective nature of the study does not allow the retrieval of reliable information on total and nocturnal hypoglycemia, whereas the incidence of severe hypoglycemia is too low to produce meaningful results on this sample size. Furthermore, the retrospective nature of the study does not allow the retrieval of information which is not part of routine clinical practice, such as an accurate study of insulin secretory status, or structured data on daily glucose profiles derived from either capillary glucose self-monitoring or continuous glucose monitoring.

Despite these limitations, the present results provide a suggestion for a simple method for the adjustment of basal and prandial insulin doses in patients with type 1 diabetes switching from glargine or detemir to degludec, which deserves further investigation.

Author contributions CL, AS, ID, and LP were involved in each of the following points: (1) data collection, (2) writing manuscript, and (3) manuscript revision. MM and EM were involved in each of the following points: (1) design; (2) analysis; (3) writing manuscript; and (4) Manuscript revision.

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Compliance with ethical standards

All the authors approved the final version of this manuscript. Dr. Edoardo Mannucci is the person who takes full responsibility for the work as a whole, including the study design, access to data, and the decision to submit and publish the manuscript

Conflict of interest The authors have no relevant conflicts of interest to declare with the exception of MM and EM: Dr. Matteo Monami (MM) and Prof. Edoardo Mannucci (EM) have received grant/speaking fees from Astra, Boehringer, MSD, Takeda, Jannsen, Sanofi, Nobonordisk, and Lilly.

Ethical approval 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.

Human and animal rights This article does not contain any studies with animal subjects.

References

1. Pettus J, Santos Cavaiola T, Tamborlane WV, Edelman S (2016) The past, present, and future of basal insulins. Diabetes Metab Res Rev 32:478–496
2. Heise T, Hermanski L, Nosek L, Feldman A, Rasmussen S, Haahr H (2012) Insulin degludec: four times lower pharmacodynamics variability than insulin glargine under steady-state conditions in type 1 diabetes. Diabetes Obes Metab 14:859–864
3. Heise T, Nosek L, Bøttcher SG, Hastrup H, Haahr H (2012) Ultra-long-acting insulin degludec has a flat and stable glucose-lowering effect in type 2 diabetes. Diabetes Obes Metab 14:944–950
4. Ratner RE, Gough SC, Mathieu C, Del Prato S, Bode B, Mersebach H, Endahl L, Zinman B (2013) Hypoglycaemia risk with insulin degludec compared with insulin glargine in type 2 and type 1 diabetes: a pre-planned meta-analysis of phase3 trials. Diabetes Obes Metab 15:175–184
5. Monami M, Mannucci E (2013) Efficacy and safety of degludec insulin: a meta-analysis of randomised trials. Curr Med Res Opin 29:339–342
6. Vora J, Christensen T, Rana A, Bain SC (2014) Insulin degludec versus insulin glargine in type 1 and type 2 diabetes mellitus: a meta-analysis of endpoints in phase 3a trials. DiabetesTher 5:435–446
7. Dżygało K, Golicki D, Kowalska A, Szypowska A (2015) The beneficial effect of insulin degludec on nocturnal hypoglycaemia and insulin dose in type 1 diabetic patients: a systematic review and meta-analysis of randomised trials. Acta Diabetol 52:231–238
8. Birkeland KI, Home PD, Wendisch U, Ratner RE, Johansen T, Endahl LA, Lyby K, Jendle JH, Roberts AP, DeVries JH, Meneghini LF (2011) Insulin degludec in type 1 diabetes: a randomized controlled trial of a new-generation ultra-long-acting insulin compared with insulin glargine. Diabetes Care 34:661–665
9. Bode BW, Buse JB, Fisher M, Garg SK, Marre M, Merker L, Renard E, Russell-Jones DL, Hansen CT, Rana A, Heller SR, BEGIN® Basal-Bolus Type 1 trial investigators (2013) Insulin degludec improves glycaemic control with lower nocturnal hypoglycaemia risk than insulin glargine in basal-bolus treatment with mealtime insulin aspart in Type 1 diabetes (BEGIN(®) Basal-Bolus Type 1): 2-year results of a randomized clinical trial. Diabet Med 30:1293–1297
10. Davies MJ, Gross JL, Ono Y, Sasaki T, Bantwal G, Gall MA, Niemeyer M, Seino H, BEGIN BB T1 Study Group (2014) Efficacy and safety of insulin degludec given as part of basal-bolus treatment with mealtime insulin aspart in type 1 diabetes: a 26-week randomized, open-label, treat-to-target non-inferiority trial. Diabetes Obes Metab 16:922–930
11. Kalra S (2013) Insulin degludec: a significant advancement in ultralong-acting Basal insulin. Diabetes Ther 4:167–173
12. Kaku K, Wolden ML, Hyllested-Winge J, Nørtoft E (2017) Insulin degludec in clinical practice: a review of Japanese real-world data. Diabetes Ther 8:189–195
13. Galasso S, Facchinetti A, Bonora BM, Mariano V, Boscari F, Cipponeri E, Maran A, Avogaro A, Fadini GP, Bruttomesso D (2016) Switching from twice-daily glargine or detemir to once-daily degludec improves glucose control in type 1 diabetes. An observational study. Nutr Metab Cardiovasc Dis 26:1112–1119
14. Heller S, Buse J, Fisher M, Garg S, Marre M, Merker L, Renard E, Russell-Jones D, Philotheou A, Francisco AM, Pei H, Bode B, BEGIN Basal-Bolus Type 1 Trial Investigators (2012) Insulin

degludec, an ultra-longacting basal insulin, versus insulin glargine in basal-bolus treatment with mealtime insulin aspart in type 1 diabetes (BEGIN Basal-Bolus Type 1): a phase 3, randomised, open-label, treat-to-target non-inferiority trial. Lancet 379:1489–1497
15. Mathieu C, Hollander P, Miranda-Palma B, Cooper J, Franek E, Russell-Jones D, Larsen J, Tamer SC, Bain SC, NN1250-3770 (BEGIN: Flex T1) Trial Investigators (2013) Efficacy and safety of insulin degludec in a flexible dosing regimen vs insulin glargine in patients with type 1 diabetes (BEGIN: Flex T1): a 26-week randomized, treat-to-target trial with a 26-week extension. J Clin Endocrinol Metab 98:1154–1162
16. Meneghini L, Atkin SL, Gough SC, Raz I, Blonde L, Shestakova M, Bain S, Johansen T, Begtrup K, Birkeland KI, NN1250-3668 (BEGIN FLEX) Trial Investigators (2013) The efficacy and safety of insulin degludec given in variable once-daily dosing intervals compared with insulin glargine and insulin degludec dosed at the same time daily: a 26-week, randomized, open-label, parallel-group, treat-to-target trial in individuals with type 2 diabetes. Diabetes Care 36:858–864
17. Zinman B, Philis-Tsimikas A, Cariou B, Handelsman Y, Rodbard HW, Johansen T, Endahl L, Mathieu C, NN1250-3579 (BEGIN Once Long) Trial Investigators (2012) Insulin degludec versus insulin glargine in insulin-naive patients with type 2 diabetes: a 1-year, randomized, treat-to-target trial (BEGIN Once Long). Diabetes Care 35:2464–2471
18. Komuro M, Inoue G, Tabata M, Yamada Y, Atsuda K, Matsubara H, Irie J, Uchida J, Nakajima C, Izumi H, Shimada M, Yamada S (2015) Insulin degludec requires lower bolus insulin doses than does insulin glargine in Japanese diabetic patients with insulin-dependent state. J Diabetes Sci Technol 9:632–638
19. Simon AC, Schopman JE, Hoekstra JB, Abu-Hanna A, Gerdes VE, Peek N, Holleman F (2015) Factors that drive insulin-dosing decisions of diabetes care providers: a vignette-based study in the Netherlands. Diabet Med 32:69–77
20. Goldman J, Kapitza C, Pettus J, Heise T (2017) Understanding how pharmacokinetic and pharmacodynamic differences of basal analog insulins influence clinical practice. Curr Med Res Opin 33:1821–1831 **(Epub ahead of print)**
21. Heise T, Hövelmann U, Nosek L, Hermanski L, Bøttcher SG, Haahr H (2015) Comparison of the pharmacokinetic and pharmacodynamic profiles of insulin degludec and insulin glargin. Expert Opin Drug Metab Toxicol 11:1193–1201
22. Porcellati F, Rossetti P, Busciantella NR, Marzotti S, Lucidi P, Luzio S, Owens DR, Bolli GB, Fanelli CG (2007) Comparison of pharmacokinetics and dynamics of the long-acting insulin analogs glargine and detemir at steady state in type 1 diabetes: a double-blind, randomized, crossover study. Diabetes Care 30:2447–2452
23. Shimoda S, Sato M, Sekigami T, Motoshima H, Yoshimura R, Fukuda K, Matsuo Y, Noda H, Okubo M, Ichimori S, Fujisawa K, Fukunaga M, Araki E, Kumamoto Insulin Degludec Observational (KIDUNA) Study Group (2016) A 1-year, prospective, observational study of Japanese outpatients with type 1 and type 2 diabetes switching from insulin glargine or detemir to insulin degludec in basal-bolus insulin therapy (Kumamoto Insulin Degludec Observational study). J Diabetes Investig 7:703–710
24. Kusunoki Y, Katsuno T, Miyakoshi K, Ikawa T, Nakae R, Ochi F, Tokuda M, Akagami T, Murai K, Miuchi M, Hamaguchi T, Miyagawa J, Namba M (2013) Effects of switching from insulin glargine or detemir to insulin degludec in patients with type 1 diabetes mellitus. Diabetes Ther 4:461–472
25. Bohn B, Zimmermann A, Wagner C, Merger S, Dunstheimer D, Kopp F, Gollisch K, Zindel V, Holl RW, DPV DPV (2017) Real-life experience of patientsstarting insulindegludec. A multicenteranalysis of 1064 subjects from the German/Austrian DPV registry. Diabetes Res Clin Pract 129:52–58
26. Dornhorst A, Lüddeke HJ, Sreenan S (2007) Safety and efficacy of insulin detemir in clinical practice: 14-week follow-up data from type 1 and type 2 diabetes patients in the PREDICTIVE European cohort. Int J Clin Pract 61:523–528
27. Porcellati F, Rossetti P, Busciantella NR, Marzotti S, Lucidi P, Luzio S, Owens DR, Bolli GB, Fanelli CG (2007) Comparison of pharmacokinetics and dynamics of the long-acting insulin analogs glargine and detemir at steady state in type 1 diabetes: a double-blind, randomized, crossover study. Diabetes Care 30:2447–2452
28. Urakami T, Kuwabara R, Habu M, Komiya K, Nagano N et al (2012) Comparison of the injection frequencies employed and basal-to-total insulin dose ratios obtained when glargine and detemir are used in children with type 1 diabetes mellitus treated by basal-bolus therapy. Diabetol Int 3:75–79