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Insulin degludec/insulin aspart (IDegAsp) treatment on glycemic control and weight in patients with insulin experienced uncontrolled type 2 diabetes mellitus: A retrospective observational study

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Objective. In this retrospective observational study, we aimed to evaluate the impact of insulin degludec/insulin aspart (IDegAsp) treatment on glycemic status, metabolic parameters, and weight/body mass index (BMI) change at a single tertiary diabetes center in Turkey.

Methods. We conducted a retrospective cohort study of patients with type 2 diabetes who received IDegAsp treatment between October 2018 and November 2019 at the diabetes outpatient clinic. The patients who had inadequate responses (HbA1c ≥8%) to at least 3 months of experienced insulin (± oral antidiabetic drug [OAD]) treatment were included into the study.

Results. One hundred patients (61% females) with a mean age of 61.7±10.0 years (range; 39–88 years) were analyzed. Mean fasting plasma glucose and HbA1c levels decreased by 3rd, 6th, 9th, and 12th months (p=0.010, p=0.007, p=0.027, and p=0.090, respectively and p<0.001, p<0.001, p<0.001, and p=0.001, respectively). Mean body weight and BMI values increased in the 3rd (83.1±15.6 kg and 31.6±5.7 kg/m2, repecitvely) and 6th (87.0±15.4 kg and 32.3±5.3 kg/m2, resepctively) months, although the changes were not statistically significant (p=0.10 and p=0.08, respectively). However, mean body weight returned to baseline levels by the 9th (80.8±17.0 kg and 30.5±6.4 kg/m2, respectively) and 12th (79.5±13.5 kg and 30.5±5.7 kg/m2, respectively) months (p=0.074 and p=0.400, respectively).

Conclusions. IDegAsp can provide a significant decrease in HbA1c in a real-life setting. Although weight gain was observed in the first months of the treatment, this effect disappeared over time and decreased to the baseline levels.

Keywords: insulin degludec, insulin aspart, glycemic control, weight change, type 2 diabetes mellitus

Diabetes mellitus (DM) is an ongoing epidemic causing a worldwide medical, social, and financial burden. The International Diabetes Federation's (IDF) Diabetes Atlas, 10th edition, demonstrates that 537 million adults are currently living with diabetes (Magliano and Boyko 2021). Treatment of diabetes has evolved in the last two decades (Satman et al. 2013). The latest practice guidelines focus on

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individual patient characteristics, including age, present comorbidities, and risk of hypoglycemia when selecting a treatment (Inzucchi et al. 2015; American Diabetes Association 2021). It is well known that insulin treatment is also associated with weight gain and this issue is a challenge with a vicious circle in treating type 2 DM (Paul et al. 2016). Therefore, in recent years, researchers have focused on antidiabetic treatment strategies that positively affect weight besides glycemic control (Meier 2012).

Insulin degludec/insulin aspart (IDegAsp) is a solvable co-formulation of two diverse insulin analogs (70% insulin degludec and 30% insulin aspart) (Ryzodeg 2025). IDegAsp is a binary-effect insulin that ensures prandial and basal glycemic control without requiring multiple injections (Kalra 2014). While the evident efficacy of IDegAsp treatment has been revealed in randomized controlled trials (RCTs) (Kumar et al. 2017; Philis-Tsimikas et al. 2019), there are limited data in real-world settings. Moreover, there are little data on IDegAsp treatment on weight change and long-term outcomes in patients with type 2 DM.

In this retrospective observational study, we aimed to evaluate the impact of IDegAsp treatment on glycemic status, metabolic parameters, and weight/body mass index (BMI) change at a single tertiary diabetes center in Turkey.

Materials and Methods

Patients. We conducted a retrospective cohort study of patients with type 2 DM who received IDegAsp treatment between October 2018 and November 2019 at the diabetes outpatient clinic of Istanbul University Faculty of Medicine. The patients' data were acquired from their charts. The patients who had inadequate responses (HbA1c ≥8) to at least 3 months of experienced insulin (± oral antidiabetic drug [OAD]) treatment were included into the study. The patients receiving only OAD treatment could not be included in the study due to the local insurance regulations in Turkey. The patients who were under 18 years of age, had type 1 DM or maturity-onset diabetes of young (MODY), lost to the follow-up, and had missing data were excluded from the study.

All procedures were performed according to the ethical standards of the Declaration of Helsinki and the National Research Committee. This study was approved by the Istanbul University Istanbul Faculty of Medicine Clinical Research Ethics Committee (approval number: 2019/1544, date: December 20, 2019).

Treatment and outcome. The patients were divided into three categories according to their prior insulin regimens: basal insulin regimen, basal-bolus insulin regimen, and biphasic insulin regimen. The basal insulin group consisted of patients receiving insulin glargine and insulin detemir. Bolus insulins used in addition to these basal insulins were aspart, lispro, glulisine, and regular human insulin. The OAD treatment was continued unless there was a contraindication and/or intolerance and was not changed during the study period.

Patients' diabetes clinical (weight and BMI values) and laboratory parameters, including fasting plasma glucose (FPG), HbA1c, estimated-glomerular filtration rate (e-GFR), low-density lipoprotein (LDL), total cholesterol (t-Col), high-density lipoprotein (HDL), triglyceride, and microalbuminuria levels were evaluated consecutively at baseline, 3rd, 6th, 9th, 12th months. The e-GFR was calculated according to the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula (Levey et al. 2009).

Statistical analysis. The study was performed using IBM SPSS-21 (Statistical Package for Social Sciences, Chicago, IL, USA). Quantitative variables were expressed as mean and standard deviation (SD) or median and interquartile range (IQR) according to the normality status. Categorical data were expressed as percentages (%) and frequencies (n). The comparison of qualitative variables was analyzed with the Pearson Chi-square test. The distribution of the data was tested with Kolmogrov-Smirnov and Shapiro-Wilk tests. The Kruskal-Wallis test was used for the analysis of continuous and more than two independent non-parametric groups (Bonferroni correction was used when necessary), and the Mann-Whitney test was used for post-hoc analysis. In the analysis of continuous and more than two independent non-parametric dependent groups, the Friedman test was used (effect size was examined using the Kendall W test), and the Wilcoxon test was used for post-hoc analysis. The results were evaluated with a 95% confidence interval, and the statistical significance level was $p<0.05$.

Results

One hundred and seventeen patients (117), who received IDegAsp treatment, were screened. Nine patients with diagnosis of type 1 DM, 2 patients with MODY, and 6 patients who lost to the follow-up were excluded from the study (Figure 1). Therefore, 100 patients with a mean age of 61.7±10.0 years (range; 39–88 years) were analyzed (61% females). The mean

Table 1
Baseline clinical and laboratory parameters of the patients

Variables	Results
Age, years, mean±SD (range)	61.7±10 (39–88)
Gender, female, n (%)	61 (61)
Duration of DM, mean±SD (range)	17.9±8.5 (1–43)
Comorbidities/complications, n (%)	
Hypertension	80 (80)
Hyperlipidemia	91 (91)
Coronary heart disease	33 (33)
Cerebrovascular accident	12 (12)
Peripheral artery disease	5 (5)
Chronic renal failure	24/96 (25)
Diabetic foot	4 (4)
Microalbuminuria	52 (52)
Retinopathy	51 (51)
Neuropathy	53 (53)
C-peptide levels, median (IQR)	1.9 (1.6)
Creatinine levels, median (IQR)	0.8 (0.4)
e-GFR, ml/min, median (IQR)	90 (43)
IDegAsp regimen, n (%)	
Single injection	16 (16)
Two injections	84 (84)

Abbreviations: DM – diabetes mellitus; e-GFR – estimated glomerular filtration rate; IDegAsp – insulin degludec/insulin aspart; IQR – interquartile range; SD – standard deviation.

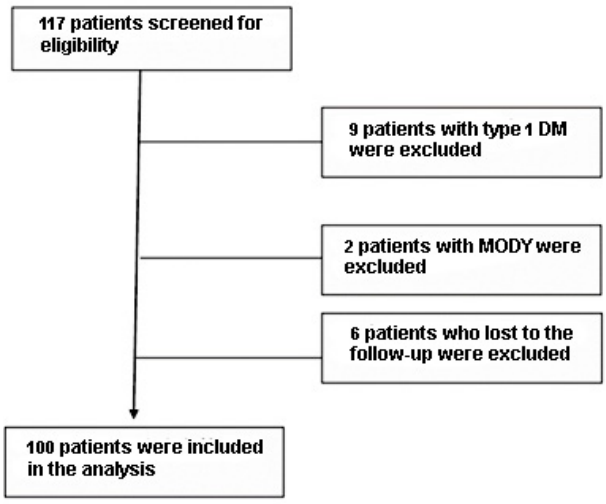

Figure 1. A flowchart of the patients participating in the study.

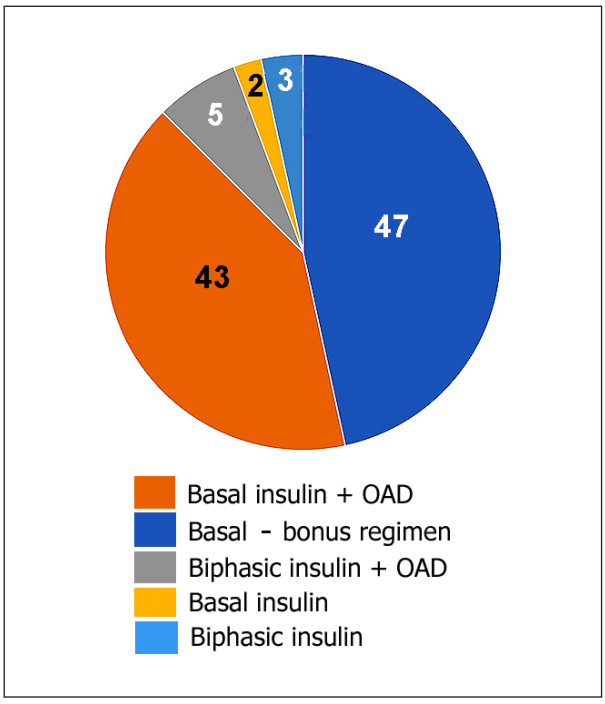

Figure 2. The distribution of the treatment history of the patients. Abbreviations: OAD - oral antidiabetic drug.

diabetes duration of patients was 17.9±8.5 years (range; 1–43 years). Before the IDegAsp treatment, the mean HbA1c level was 10.4±1.9%, FPG was 214±95 mg/dL, body weight was 82.8±16.6 kg, and BMI was 30.6±6.2 kg/m^2. Clinical and laboratory features of the patients were described in Table 1. While the majority of patients were on a basal-bolus regimen (47%), 43% of patients were on basal insulin + OAD, 5% were on biphasic insulin + OAD, 3% were on biphasic insulin, and 2% were on basal insulin. (Figure 2).

Mean FPG and HbA1c levels decreased by 3rd, 6th, 9th, and 12th months (p=0.01, p=0.007, p=0.027, and p=0.09, respectively and p<0.001, p<0.001, p<0.001, and p=0.001, respectively). While LDL and t-Col levels decreased in the 3rd month (p=0.023 and p=0.009, respectively), HDL levels decreased in the 9th month (p=0.026) but other values were not different compared to baseline levels (Table 2).

Mean body weight and BMI values increased in the 3rd (83.1±15.6 kg and 31.6±5.7 kg/m^2, respectively) and 6th (87±15.4 kg and 32.3±5.3 kg/m^2, respectively) months, although the changes were not statistically significant (p=0.1 and p=0.08, respectively). However, mean body weight returned to baseline levels by the 9th (80.8±17 kg and 30.5±6.4 kg/m^2, respectively) and 12th (79.5±13.5 kg and 30.5±5.7 kg/m^2, respectively) months (p=0.074 and p=0.4, respectively). The median (IQR) total injection count decreased from 2 (3) to 2 (1) (p<0.001) with IDegAsp compared

Table 2
Clinical and laboratory changes of the participants during to the study

Variables	Baseline	3rd month	6th month	9th month	12th month	p1	p2	p3	p4
Body weight, mean±SD	82.8±16.6	83.1±15.6	87.0±15.4	80.8±17.0	79.5±13.5	0.100	0.080	0.074	0.400
BMI, mean±SD	30.6±6.2	31.6±5.7	32.3±5.3	30.5±6.4	30.5±5.7	0.044	0.100	0.370	0.800
Fasting plasma glucose, mean±SD	214.0±95.0	170.8±60.0	181.6±75.0	163.2±64.0	184.4±79.0	0.010	0.007	0.027	0.090
HbA1c, %, mean±SD	10.40±1.96	8.70±1.50	8.60±1.60	8.96±1.40	9.50±2.00	<0.001	<0.001	<0.001	0.001
LDL-C, mean±SD	119.8±37.7	111.9±33.5	109.8±28.3	118.7±36.5	105.4±30.0	0.023	0.100	0.400	0.054
HDL-C, mean±SD	42.9±13.7	42.2±12.3	42.2±11.6	41.9±13.8	43.5±12.5	0.064	0.500	0.026	0.200
Total-C, mean±SD	201.6±46.7	190.0±42.3	190.3±52.5	203.4±55.5	179.5±34.0	0.009	0.150	0.060	0.300
Triglycerides, mean±SD	255.0±116.0	200.0±127.0	209.5±154.0	224.6±138.0	165.2±75.0	0.150	0.300	0.200	0.160
Microalbumin/creatinine, median (IQR)	48 (150)	27.5 (170)	52.5 (418)	45 (522)	152.5 (628)	0.500	0.600	0.074	0.007
e-GFR, median (IQR)	90 (43)	89.8 (35)	81 (46)	83.5 (35)	79 (34)	0.500	0.700	0.030	0.130

Abbreviations: BMI – body mass index; e-GFR – estimated glomerular filtration rate; HbA1c – hemoglobin A1C; HDL-C – high-density lipoprotein cholesterol; IQR – interquartile range; LDL-C – low-density lipoprotein cholesterol; SD – standard deviation; total-C – total cholesterol. p1 – significance between baseline and 3rd month; p2 – significance between baseline and 6th month; p3 – significance between baseline and 9th month; p4 – significance between baseline and 12th month; bold values are statistically significant.

Table 3
Change of insulin requirements during the study period

Variables	Baseline	12th months	p-value
Total injection counts, median (IQR)	2 (3)	2 (1)	<0.001
Total insulin dose (IU), median (IQR)	47 (38)	43 (27.3)	0.001
Basal insulin dose (IU), median (IQR)	36 (23)	28 (18)	<0.001
Bolus insulin dose (IU), median (IQR)	28 (18)	25.4 (8.8)	<0.001

Abbreviations: IQR – interquartile range. Bold values are statistically significant.

to the prior treatment. Median (IQR) daily total (47 [38] vs. 43 [27.3] IU; p=0.001), basal (36 [23] vs. 28 [18] IU; p<0.001), and bolus (28 [18] vs. 25.4 [8.8] IU; p<0.001) insulin doses decreased compared to baseline (Table 3).

Discussion

In this retrospective cohort study, we aimed to evaluate the effect of IDegAsp on the glycemic control, clinical and laboratory parameters, and weight/BMI changes in a real-world setting. IDegAsp treatment was associated with a better glycemic control and improved levels of HbA1c and FPG compared to the prior treatment. While IDegAsp treatment was associated with weight gain in the first 6 months, this effect disappeared after 6th month and returned to baseline levels by the 12th month.

The efficacy and safety of IDegAsp treatment were shown compared to various insulin regimens. A randomized controlled trial (RCT) revealed a better HbA1c improvement with IDegAsp compared to a basal insulin regimen (Cho et al. 2020). Recent studies have demonstrated that IDegAsp was non-inferior regarding glycemic control compared to insulin glargine U_{100} (Christiansen et al. 2016). Moreover, Onishi et al. (2013) reported superiority with IDegAsp compared to insulin glargine. Furthermore, a meta-analysis concluded that IDegAsp treatment provided better glycemic control and lower hypoglycemia risk than the basal-bolus regimen (Edina et al. 2022). IDegAsp treatment was also found to be safe and effective in real-world data (Kisioglu et al. 2021; Mohamed et al. 2023). Although the efficacy of IDegAsp on glycemic control is evident, observing the effect of IDegAsp on weight change is a challenge in RCTs due to their shorter follow-up. Real-word data with long-term follow-up studies are important to interpret the long-term safety and efficacy as well as change in anthropometric values such as weight and BMI of relatively new treatment modalities. In our study, although significant glycemic control including FPG and HbA1c was reached as quickly as the 3rd month, it continued 6th and 9th months but partially deteriorated by the 12th month. In our study,

the reduced efficacy of insulin treatment may be due to a decrease in treatment adherence or motivation of the patients with DM or a decrease in c-peptide reserve over time.

In our study, we also established reduced cumulative insulin doses besides better glycemic control with IDegAsp compared to other insulin modalities. This issue is important to prevent weight gain as well as reduce treatment costs (Luo et al. 2022). Weight gain is a well-known complication of insulin treatment which is associated with deterioration in metabolic parameters and increased insulin doses (DCCT Research Group 1988; Aas et al. 2009). Lower weight gain is possibly due to lower doses of insulin requirement with IDegAsp compared to the previous insulin regimens. Furthermore, an RCT revealed a lower weight gain compared to NPH insulin even though total insulin doses were not different, which was thought to be associated with lower leptin as well as lower energy intake in patients with type 1 DM (Zachariah et al. 2011). Better weight outcomes with insulin degludeg may also be due to reduced blood glucose variability and a reduced risk of hypoglycemia compared to NPH insulin (Vague et al. 2003). On the other hand, lesser weight gain with insulin detemir compared to NPH insulin was independent of hypoglycemia in a study (Davies et al. 2008). In the former study, the insulin detemir group had a 1.2 kg weight gain compared to NPH with 2.8 kg ($p<0.001$) at the 26-week follow-up. In our study, although this difference was higher with an average of 4 kg by the 6^{th} month but decreased by the 12^{th} to the baseline levels. Further studies with long-term follow-up are needed to clarify the relationship between insulin IDegAsp treatment and weight change.

The main limitation of the study is its retrospective design. Additionally, the absence of a control group and missing data due to the retrospective design of the study were other limitations. The strength of our study is that the single center is a tertiary center, meaning that patients were referred due to failure to reach glycemic targets.

Conclusion

IDegAsp can provide a significant decrease in HbA1c in a real-life setting. Although weight gain was observed in the first months of the treatment, this effect disappeared over time and decreased to the baseline levels. This study suggests that even if there is weight gain in the first months of IDegAsp treatment in patients with type 2 DM, this effect may disappear over time and the treatment may not be discontinued for this reason.

References

Aas AM, Ohrvik J, Malmberg K, Ryden L, Birkeland KI. Insulin-induced weight gain and cardiovascular events in patients with type 2 diabetes. A report from the DIGAMI 2 study. Diabetes Obes Metab 11, 323–329, 2009.

American Diabetes Association. 9. Pharmacologic approaches to glycemic treatment: standards of medical care in diabetes-2021. Diabetes Care 44, S111–124, 2021.

Cho KY, Nakamura A, Oba-Yamamoto C, Tsuchida K, Yanagiya S, Manda N, Kurihara Y, Aoki S, Atsumi T, Miyoshi H. Switching to once-daily insulin degludec/insulin aspart from basal insulin improves postprandial glycemia in patients with type 2 diabetes mellitus: randomized controlled trial. Diabetes Metab J 44, 532–541, 2020.

Christiansen JS, Home P, Kumar A. IDegAsp (insulin degludec + insulin aspart) for the management of type 2 diabetes: current status. Expert Rev Endocrinol Metab 11, 103–111, 2016.

Davies MJ, Derezinski T, Pedersen CB, Clauson P. Reduced weight gain with insulin detemir compared to NPH insulin is not explained by a reduction in hypoglycemia. Diabetes Technol Ther 10, 273–277, 2008.

DCCT Research Group. Weight gain associated with intensive therapy in the diabetes control and complications trial. Diabetes Care 11, 567–573, 1988.

Edina BC, Tandaju JR, Wiyono L. Efficacy and safety of insulin degludec/insulin aspart (IDegAsp) in type 2 diabetes: systematic review and meta-analysis. Cureus 14, e25612, 2022.

Inzucchi SE, Bergenstal RM, Buse JB, Diamant M, Ferrannini E, Nauck M, Peters AL, Tsapas A, Wender R, Matthews DR. Management of hyperglycemia in type 2 diabetes, 2015: a patient-centered approach - update to a position statement of the American Diabetes Association and the European Association for the Study of Diabetes. Diabetes Care 38, 140–149, 2015.

Kalra S. Insulin degludec aspart: the first co-formulation of insulin analogues. Diabetes Ther 5, 65–72, 2014.

Kisioglu SV, Demir AS, Tufekci D, Emur Gunay Y, Coskun H, Ucuncu O, Nuhoglu I, Kocak M, Karakullukcu S, Ersoz HO. Clinical research of insulin glargine U300 basal-bolus therapy and insulin degludec/aspart co-formulation in type 2 diabetes mellitus: A real world experience. Int J Clin Pract 75, e14377, 2021.

Kumar S, Jang HC, Demirag NG, Skjoth TV, Endahl L, Bode B. Efficacy and safety of once-daily insulin degludec/insulin aspart compared with once-daily insulin glargine in participants with type 2 diabetes: a randomized, treat-to-target study. Diabet Med 34, 180–188, 2017.

Levey AS, Stevens LA, Schmid CH, Zhang YL, Castro AF, 3rd, Feldman HI, Kusek JW, Eggers P, Van Lente F, Greene T, Coresh J, CKD-ERPI. A new equation to estimate glomerular filtration rate. Ann Inter Med 150, 604–612, 2009.

Luo Q, Zhou L, Zhou N, Hu M. Cost-effectiveness of insulin degludec/insulin aspart versus biphasic insulin aspart in Chinese population with type 2 diabetes. Front Public Health 10, 1016937, 2022.

Magliano DJ, Boyko EJ. IDF Diabetes Atlas 10th Edition Scientific Committee: Diabetes Atlas. In., 10th ed. Brussels, Belgium, International Diabetes Federation, 2021.

Meier JJ. GLP-1 receptor agonists for individualized treatment of type 2 diabetes mellitus. Nat Rev Endocrinol 8, 728–742, 2012.

Mohamed M, Lim SC, Mumtaz M, Uppal S, Mukherjee D, Kassim MSM, Sreedharan S, Doraiswamy AM, Chong KM, Tat LY, Nordin SB, Giek JLH, Hussein Z, Kadir KA, Lau BK, Chan SP. Initiating or switching to insulin degludec/insulin aspart in adults with type 2 diabetes in Malaysia: results from a prospective, non-interventional real-world study. J ASEAN Fed Endocr Soc 38, 37–44, 2023.

Onishi Y, Ono Y, Rabol R, Endahl L, Nakamura S. Superior glycaemic control with once-daily insulin degludec/insulin aspart versus insulin glargine in Japanese adults with type 2 diabetes inadequately controlled with oral drugs: a randomized, controlled phase 3 trial. Diabetes Obes Metab 15, 826–832, 2013.

Paul SK, Shaw JE, Montvida O, Klein K. Weight gain in insulin-treated patients by body mass index category at treatment initiation: new evidence from real-world data in patients with type 2 diabetes. Diabetes Obes Metab 18, 1244–1252, 2016.

Philis-Tsimikas A, Astamirova K, Gupta Y, Haggag A, Roula D, Bak BA, Fita EG, Nielsen AM, Demir T. Similar glycaemic control with less nocturnal hypoglycaemia in a 38-week trial comparing the IDegAsp co-formulation with insulin glargine U100 and insulin aspart in basal insulin-treated subjects with type 2 diabetes mellitus. Diabetes Res Clin Pract 147, 157–165, 2019.

Ryzodeg. European Medicines Agency: European public assessment report (EPAR) - Product information, available at https://www.ema.europa.eu/en/medicines/human/EPAR/ryzodeg, last update on 04/03/2025.

Satman I, Omer B, Tutuncu Y, Kalaca S, Gedik S, Dinccag N, Karsidag K, Genc S, Telci A, Canbaz B, Turker F, Yilmaz T, Cakir B, Tuomilehto J, TURDEP-II Study Group. Twelve-year trends in the prevalence and risk factors of diabetes and prediabetes in Turkish adults. Eur J Epidemiol 28, 169–180, 2013.

Vague P, Selam JL, Skeie S, De Leeuw I, Elte JW, Haahr H, Kristensen A, Draeger E. Insulin detemir is associated with more predictable glycemic control and reduced risk of hypoglycemia than NPH insulin in patients with type 1 diabetes on a basal-bolus regimen with premeal insulin aspart. Diabetes Care 26, 590–596, 2003.

Zachariah S, Sheldon B, Shojaee-Moradie F, Jackson NC, Backhouse K, Johnsen S, Jones RH, Umpleby AM, Russell-Jones DL. Insulin detemir reduces weight gain as a result of reduced food intake in patients with type 1 diabetes. Diabetes Care 34, 1487–1491, 2011.