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ORIGINAL ARTICLE

Not All Type-2-Diabetes Patients Increase Body Mass Index After Initiating Insulin: Results of Latent Class Analysis from the DPV Registry

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Abstract

Background: Is insulin initiation linked to increasing body mass index (BMI) in all patients with type-2-diabetes (T2D)? To determine distinct longitudinal patterns of BMI change over time.
Materials and Methods: 5057 patients with T2D (55% males, median BMI [IQR]: 30.0 [26.9–33.3] kg/m^2) aged ≥40 years at diabetes diagnosis and with ≥2 years of follow-up after insulin initiation irrespective of previous or concurrent use of metformin/dipeptidyl peptidase-4-inhibitor from the multicenter prospective diabetes registry DPV were studied. To identify subgroups following a similar pattern of BMI change after insulin initiation, longitudinal group-based trajectory modeling was applied. Multinomial logistic regression was then used to analyze covariates associated with group membership.
Results: Three heterogeneous groups with either relevant *BMI increase* (delta-BMI: +4.0 kg/m^2 after 2 years; 12% of patients); *slight BMI increase* (+0.4 kg/m^2; 80%); or *BMI decrease* (−3.2 kg/m^2; 8%) were identified. Patients with older age [OR (95% CI): 1.37 (1.11–1.69)] and obesity [2.05 (1.65–2.55)] before insulin start were more often in the *BMI decreasing* group, and less often in the *BMI increasing* class [0.80 (0.67–0.95); 0.82 (0.69–0.98)]. A worse HbA1c both at insulin start and during follow-up [1.90 (1.60–2.26); 1.17 (1.07–1.27)], a higher insulin dose [1.67 (1.33–2.10)], and severe hypoglycemic events [2.38 (1.60–3.53)] after insulin initiation were all linked with higher odds of belonging to the *BMI increasing* trajectory.
Conclusions: Patient heterogeneity with respect to weight gain after initiation of insulin therapy in adult T2D was detected by an objective computer algorithm. Older people with obesity should not defer from insulin use due to fear of weight gain.

Keywords: Type-2-diabetes, Insulin initiation, BMI change, Group-based modeling.

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Introduction

The start of insulin treatment is often linked with weight gain.[1] Therefore, patients with type-2-diabetes (T2D) being overweight or obese often are reluctant to use insulin either alone or in combination with other glucose-lowering medication. Nevertheless, insulin treatment is recommended by national and international guidelines if individual treatment target cannot be achieved with lifestyle management and other glucose-lowering substances, although potential weight gain, risk of hypoglycemia, costs, and other patient-related preferences should be considered.[2,3]

Insulin-associated weight gain should be limited in T2D, where more than 90% of patients are already overweight or obese. Additional weight gain contributes to further reduction of insulin sensitivity and in turn increases exogenous insulin requirements to high doses. The ability to predict individuals most at risk for insulin-associated weight gain would be a major clinical benefit not only with respect to personalize diabetes therapy but also to address patient fear of additional weight gain and reluctance to initiate insulin—which in turn increases the risk of diabetes-related complications at a later time.

A relatively new statistical technique in medical studies to analyze longitudinal data is group-based trajectory (GBT) modeling that allows the identification of unique subgroups of patients, classified according to the pattern of change of body mass index (BMI) over time. The identified subgroups can be characterized subsequently.[4]

The aim of this study was to investigate the heterogeneity of BMI trajectories (BMI changes) after commencing insulin in a large cohort of adult patients with T2D from routine care documented in the standardized diabetes patient follow-up registry, DPV from Germany and Austria. In addition, we evaluated whether the identified subgroups can be individually characterized by demographic and insulin-related parameters.

Materials and Methods

DPV registry

Since 1995, a nationwide initiative for the standardized documentation of routinely assessed demographic and diabetes-related data from specialized diabetes care centers exists in Germany. Meanwhile (March 2020), also centers from other countries like Austria participate and a network of 474 collaborating centers has emerged with a total of 586,895 patients with diabetes documented of all ages. Every half-year, the locally documented data are transmitted pseudonymized to Ulm University, Germany. After plausibility has been proven, the data are aggregated into an anonymized cumulative database, called the diabetes patient follow-up registry, DPV (www.d-p-v.eu).[5] The Ethics Committee of Ulm University has approved the DPV initiative and the local Review Boards of each participating center of the pseudonymized data collection.

Study cohort

All patients with T2D aged 40 years or older at diabetes diagnosis with start of insulin treatment at least 1 year after diabetes diagnosis were included. Further inclusion criteria were a minimum follow-up of 2 years with at least one documented BMI value within the last half-year before insulin start and three or more BMI values during follow-up. Multiple values were aggregated per patient on the basis of 6-month intervals. To consider potential changes of diabetes therapy, insulin treatment needed to be documented at a minimum of three aggregated time-points during follow-up.

Patients with late onset autoimmune diabetes were excluded, also patients using antidepressive medication and/or systemic steroids and/or having renal dysfunction (defined as glomerular filtration rate eGFR <30 mL/min/1.73 m^2 and/or renal dialysis and/or renal transplantation) during the observation period (half-year before insulin start and up to 2 years after insulin initiation). Further, patients with any malignant tumor, bariatric surgery, and/or the use of anticontraceptives during the observation period were excluded. Any diagnosis of depression, seizure disorder, and/or schizophrenia during the individual's life course was further in the exclusion criteria. To exclude underweight and morbid obesity with potential to undergo bariatric surgery, patients with a baseline BMI value ≤ 17.5 or >40 kg/m^2 were excluded as well. Patients using oral antidiabetics other than metformin or dipeptidyl peptidase-4 (DPP-4) inhibitors during the observation period were precluded from analysis.

The final study cohort comprised 5057 patients.

Variables of interest

To analyze the change of BMI, delta-BMI was calculated as the difference of BMI at the time-point [*i*] minus baseline BMI. Delta-BMI was used as trajectory outcome variable with duration since the start of insulin as underlying time scale.

Demographics such as age at insulin start and sex were studied in relationship to BMI group membership. Metabolic control assessed by hemoglobin A1c (HbA1c) and several insulin-related data were further covariates.

The type of insulin regimen was categorized as (i) basal supported oral therapy (BOT; basal insulin only) or supplementary insulin therapy (prandial insulin only) or unknown; (ii) conventional insulin therapy (prandial and basal insulin combined; 1–3 injection time-points); and (iii) intensified conventional insulin therapy (ICT; prandial and basal insulin combined; 4–8 injection time-points) or continuous subcutaneous insulin infusion.

Insulin preparations were categorized as long-acting insulin analogs (detemir, glargine U100, glargine U300, degludec), neutral protamine Hagedorn (NPH) insulin, short-acting insulin analogs (aspart, faster aspart, glulisine, lispro, lispro U200), and regular insulin. In addition, total daily insulin dose, basal/prandial insulin dose each per kilogram body weight, as well as other concomitant glucose-lowering medication (metformin, DPP-4) were studied.

The frequency of severe hypoglycemia over 2 years of follow-up was also analyzed. According to the American Diabetes Association, severe hypoglycemia was defined as ''an event requiring assistance by another person to actively administer carbohydrates, glucagon, or other resuscitative actions.''[6]

The multiple of the mean method was applied to mathematically standardize center-based HbA1c values to the Diabetes Control and Complications Trial (4.05%–6.05% [20.7–42.6 mmol/mol]).[7]

Statistical methods

To identify distinct subgroups of patients with comparable BMI change over time after the initiation of insulin, the GBT technique based on Nagin was applied.[8] This semiparametric statistical technique assumes that there are heterogeneous latent clusters within a population and that each patient follows a unique pattern of BMI change. Contrary to many other statistical techniques where the number of subgroups has to be defined ''a priori,'' the GBT method uses a forward stepwise process, starting with one group and then adding further groups to select the model with the optimal number of subgroups.

To determine the optimal number of unique patterns, the Bayes information criterion (BIC, the lower the better) was used and any given subgroup had to include at least ≥5% of the study population. Model parameters were estimated by the maximum likelihood technique and identified trajectories were fitted using quadratic and cubic terms. The method has been previously used by the DPV group.[4]

The GBT was additionally applied for both sexes as well as for different age groups (40 to <50 years at diabetes onset; ≥50 years at diabetes onset) and patients with obesity (BMI ≥30 kg/m^2) separately. Moreover, additional separate analyses were carried out for patients on ''basal only insulin,'' ''prandial only insulin'' and ''basal-bolus insulin therapy.''

Unadjusted comparisons between groups were performed applying Kruskal-Wallis or χ^2-tests. Due to multiple tests per trajectory class, the step-down Bonferroni procedure (Holm method) was used to correct *P*-values. A two-sided *P*-value <0.05 was considered significant.

In addition, multinomial logistic regression analyses were applied to evaluate which covariates are associated with group membership. A basic model included age at insulin initiation (≤70 years vs. >70 years), sex, BMI (<30 kg/m^2 vs. ≥30 kg/m^2), and HbA1c (≤7.5% vs. >7.5%) prior insulin start as covariates. Further covariates within the first half-year after insulin initiation or during 2 years of follow-up (severe hypoglycemia) were added, each in a separate model.

The statistical software package SAS was used for all analyses with the PROC TRAJ macro for trajectory analysis (SAS Institute, Inc., Cary, NC).

Results

Baseline characteristics of the study cohort are summarized in Table 1. Insulin was initiated at a median [IQR] age of 68.7 [62.0; 75.3] years and the median BMI before insulin start was in the overweight/obese range (30.0 [26.9; 33.3] kg/m^2).

Table 1. Description of Entire Study Cohort and Separated by Trajectory Class

	All (n = *5057*)	*BMI decrease* (n = *396*)	*BMI slight increase* (n = *4029*)	*BMI increase* (n = *632*)
Age at T2D onset, years	55.8 [49.2; 62.7]	56.5 [50.3; 63.5]	55.9 [49.3; 62.7]	54.4 [48.0; 62.5]
Males, %	55.0	49.5	55.5	52.2
Age at insulin start, years	68.7 [62.0; 75.3]	70.5 [63.0; 77.6]	68.8 [62.2; 75.2]	67.4 [59.6; 74.0][a]
Prior insulin start[b]				
BMI, kg/m^2	30.0 [26.9; 33.3]	31.8 [28.8; 35.0][a]	29.9 [26.8; 33.1]	29.4 [26.6; 33.2]
Height, cm	169 [162; 176]	168.0 [161.0; 175.0]	169.0 [162.0; 176.0]	168.5 [162.0; 176.0]
HbA1c, %	7.5 [6.8; 8.5]	7.3 [6.7; 8.4]	7.5 [6.7; 8.4]	8.1 [7.2; 9.5][a]
First half-year after insulin start[c]				
BMI, kg/m^2	30.1 [27.0; 33.4]	30.4 [27.3; 33.3]	29.9 [26.8; 33.2]	31.0 [27.9; 34.9]
Height, cm	168.0 [162.0; 176.0]	168.0 [162.0; 175.0]	169.0 [162.0; 176.0]	168.0 [161.7; 175.0]
HbA1c, %	7.0 [6.5; 7.7]	6.8 [6.3; 7.5][a]	7.0 [6.4; 7.7]	7.2 [6.6; 8.1][a]
Total insulin dose, IU/kg·day	0.49 [0.30; 0.74]	0.52 [0.28; 0.74]	0.48 [0.29; 0.72]	0.57 [0.37; 0.82][a]
Prandial dose, IU/kg·day	0.33 [0.21; 0.49]	0.32 [0.19; 0.54]	0.33 [0.21; 0.49]	0.37 [0.24; 0.53][a]
Basal dose, IU/kg·day	0.26 [0.16; 0.37]	0.27 [0.16; 0.39]	0.26 [0.16; 0.37]	0.27 [0.18; 0.40]
Short-acting insulin analogs, %	44.1	43.6	43.6	47.1
Long-acting insulin analogs, %	43.0	39.2	43.3	43.4
SIT/BOT/unknown, %	40.8	42.9	41.1	37.0
CT, %	18.3	19.7	17.9	19.8
ICT/CSII, %	40.9	37.4	40.9	43.2
Metformin, %	28.5	29.7	28.3	28.8
DPP-4, %	11.6	14.2	11.7	9.3
After 2 years of follow-up				
Severe hypoglycemia[d], %	2.9	3.3	2.5	5.7[a]
HbA1c[e], %	6.9 [6.4; 7.6]	6.8 [6.1; 7.7]	6.9 [6.4; 7.6]	7.1 [6.5; 7.9][a]

Median with quartiles or proportion.
[a]$P < 0.05$ for comparison with *BMI slight increase* group.
[b]Multiple values 6 months prior insulin initiation were aggregated.
[c]Multiple values during the first 6 months after insulin initiation were aggregated.
[d]Considers all events over 2 years after the start of insulin.
[e]Multiple values during the last 6 months of the observation period were aggregated.
BMI, body mass index; BOT, basal supported oral therapy; CSII, continuous subcutaneous insulin infusion; CT, conventional insulin therapy; DPP-4, dipeptidyl peptidase-4; HbA1c, hemoglobin A1c; ICT, intensified conventional insulin therapy; SIT, supplementary insulin therapy.

Three distinct trajectories of BMI change

Applying the GBT approach, three distinct groups of BMI change up to 2 years after the start of insulin irrespective of metformin/DPP-4 medication were identified (Fig. 1). Group 1 (dashed-dotted line, 7.8% of patients) included subjects with continuous *BMI decrease* an average up to −3.2 kg/m^2 at 2 years after initiation of insulin. Patients with only *slight BMI increase* over the observation period represent group 2 (continuous line, 79.7% of patients), whereas patients with a relevant *BMI increase* (average delta-BMI: +4.0 kg/m^2 at 2 years after insulin initiation) were included in group 3 (dashed line, 12.5% of patients).

Demographic and basic clinical description of each trajectory class and the entire cohort are given in Table 1.

The selection of the optimal number of clusters was based on BIC and a minimum group size of 5% of the patient cohort. Starting from a one-class model, BIC decreased continuously up to a three-class model (BIC_1: 44,219; BIC_2: 40,904; BIC_3: 38,260). Although a four-class model revealed an even lower BIC (36,808), the additional criterion of a sufficient cluster size was no longer be valid. The final BIC of the fitted model was 38,267.

Which demographic and clinical features are related to group membership?

Multinomial logistic regression indicated in a basic model (ref. group: *slight BMI increase* trajectory), age at start of insulin, BMI, and HbA1c before insulin start as relevant covariates associated with group membership; whereas for sex, no significant relationship could be observed (Fig. 2). A worse HbA1c above the recommended target before insulin start was related with a higher odds of belonging to the *BMI increasing* trajectory, whereas older age and a BMI at baseline in the obese range were linked with lower odds. By contrast, older age and particularly a BMI in the obese range before insulin start were both associated with a higher odds of belonging to the *BMI decreasing* class.

Regarding the covariates during follow-up, increasing HbA1c or total daily insulin dose within the first half-year after insulin start were both related with a higher odds of belonging to the *BMI increasing* trajectory. Moreover, a higher HbA1c at the end of the observation period and the presence of severe hypoglycemia within the first 2 years after insulin start were linked with higher odds. By contrast, a higher HbA1c during the first half-year after insulin initiation was related to a lower odds of belonging to the *BMI decreasing* class.

For all other covariates (i.e., type of insulin regimen, insulin preparation, basal or prandial insulin dose and metformin/DPP-4 use), no clinically relevant association with group membership could be identified (data not shown).

Stratified trajectory analyses by sex, age group, and obesity status

Applying the GBT approach separately to specific age groups (40 to <50 and ≥50 years at diabetes onset), for both sexes or solely for patients with obesity (BMI ≥30 kg/m^2), revealed again three heterogenous trajectories with very similar developmental curves of delta-BMI after insulin initiation. Respective proportions were similar to the overall cohort, where the majority of patients belong to the *slightly BMI increasing* class (Table 2). The extent of average BMI increase/decrease at 2 years after insulin initiation is summarized for the stratified analyses in Table 2.

Trajectory analysis in a group of patients with insulin therapy only

The GBT approach was also applied in patients ($n = 2767$) who received no oral antihyperglycemic therapy in addition to insulin during the observation period. Again, three heterogenous clusters of BMI change after the start of insulin therapy were identified with very similar patterns to the initial study cohort (Supplementary Fig. S1). Group sizes as well as the average BMI decrease/increase at 2 years after insulin initiation were also comparable to the initial study cohort.

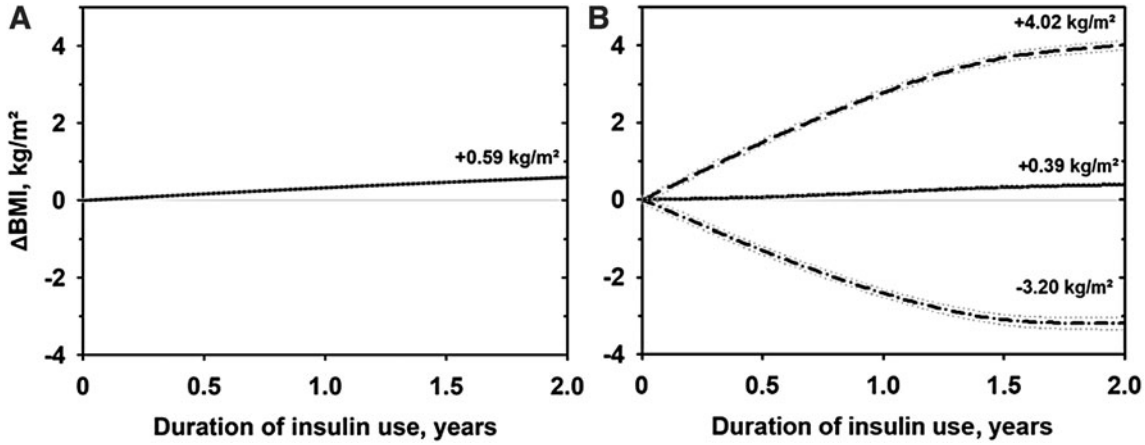

FIG. 1. **(A)** Delta-BMI trajectory (95% CI) and **(B)** three distinct delta-BMI trajectories of 5057 patients with type 2 diabetes over 2 years after starting insulin therapy irrespective of metformin and/or DPP-4 inhibitor use. Delta-BMI was calculated as aggregated BMI at respective time-point minus baseline BMI. **(A)** Continuous line (100% of patients); **(B)** dashed line (12.5%); continuous line (79.7%), dash-dotted line (7.8%). Gray dotted lines represent the 95% confidence interval. BMI, body mass index; DPP-4, dipeptidyl peptidase-4.

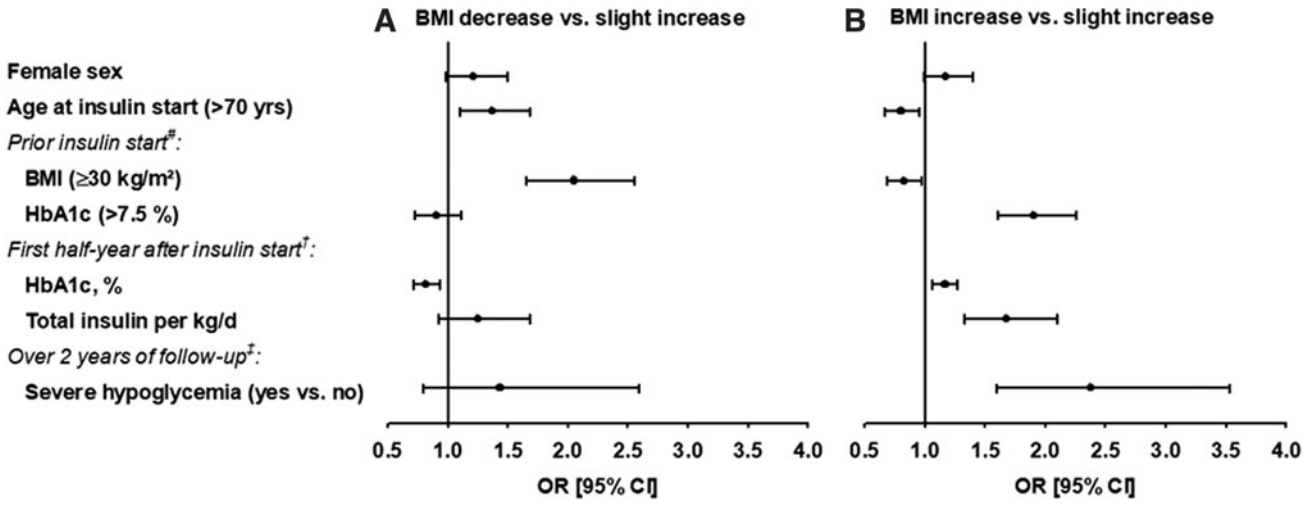

FIG. 2. Covariates related with group membership for **(A)** the BMI decreasing and **(B)** the BMI increasing group versus the BMI slightly increasing group at different time-points prior and after insulin start irrespective of metformin/DPP-4 inhibitor use. Odds ratios with 95% CI were estimated from multinomial logistic regression models, including different sets of covariates. For continuous variables, data are given per one unit increase of covariate. A basic model included sex, age at insulin start (≤70 years vs. >70 years), BMI (<30 kg/m^2 vs. ≥30 kg/m^2), and HbA1c (≤7.5% vs. >7.5%) prior insulin start as covariates. All other variables were added each in a separate model. #Multiple values 6 months prior insulin initiation were aggregated; †multiple values during the first 6 months after insulin initiation were aggregated; ‡considers all events over 2 years after the start of insulin.

Trajectory analyses in groups of patients with basal insulin only, prandial insulin only, or basal-bolus insulin therapy

Applying the GBT technique in patients on basal only insulin ($n=1460$), prandial only insulin ($n=976$) or basal-bolus insulin therapy ($n=4036$) revealed in all three cohorts again three heterogeneous subgroups of patients with similar BMI change over time compared to the initial study cohort. However, the extent of BMI change differed depending on the type of cohort. As expected, patients on ''basal only insulin'' experienced the lowest BMI increase compared to patients on ''prandial insulin only'' with overall the greatest BMI increase (Table 2).

Discussion

To the best of our knowledge, this study is the first revealing three distinct groups of heterogenous delta-BMI trajectories in patients with T2D after the start of insulin irrespective of concomitant metformin/DPP-4 use. Contrary to the commonly assumed homogeneous BMI increase with insulin initiation, nearly 80% of patients experienced only a *slight BMI increase* up to 2 years after insulin start. Nevertheless, two smaller outlier groups exist with either considerable *BMI increase* or with *BMI decrease*. Being of younger age, nonobese and having a worse metabolic control at insulin start as well as increasing HbA1c, higher initial insulin dose, and severe hypoglycemic events during insulin use were all related with clear *BMI increase*.

Table 2. Group Sizes and Average Delta-Body Mass Index at 2 Years After Insulin Start of Various Additional Analyses

	BMI decrease		*BMI slight increase*		*BMI increase*	
Additional analysis	*%*	*$\Delta BMI_{2\ years}$*	*%*	*$\Delta BMI_{2\ years}$*	*%*	*$\Delta BMI_{2\ years}$*
By age group at diabetes diagnosis						
40 to <50 years	9.9	−2.62 (−2.89 to −2.33)	76.5	+0.65 (+0.57 to +0.72)	13.6	+4.34 (+4.14 to +4.54)
≥50 years	7.4	−3.51 (−3.69 to −3.33)	80.1	+0.31 (+0.26 to +0.36)	12.6	+3.91 (+3.78 to +4.05)
By sex						
Females	8.0	−3.41 (−3.64 to −3.19)	80.0	+0.38 (+0.32 to +0.44)	11.9	+4.45 (+4.27 to +4.63)
Males	8.4	−3.06 (−3.26 to −2.86)	77.9	+0.43 (+0.38 to +0.49)	13.7	+3.74 (+3.60 to +3.88)
By obesity status						
BMI ≥30 kg/m^2	9.0	−3.89 (−4.08 to −3.69)	79.6	+0.35 (+0.29 to +0.42)	11.4	+4.20 (+4.01 to +4.39)
By insulin therapy						
Basal only	8.6	−2.85 (−3.12 to −2.59)	76.6	+0.23 (+0.15 to +0.31)	14.8	+3.40 (+3.21 to +3.60)
Prandial only	10.4	−2.98 (−3.32 to −2.64)	82.5	+0.58 (+0.47 to +0.69)	7.0	+5.46 (+4.99 to +5.93)
Basal-bolus	7.7	−3.34 (−3.51 to −3.17)	77.6	+0.38 (+0.33 to +0.43)	14.8	+3.75 (+3.63 to +3.87)

Data are given as proportion or mean with 95% CI. $\Delta BMI_{2\ years}$ represents the average BMI increase/decrease at 2 years after insulin initiation.

The widely reported insulin-associated weight gain up to 3 to 9 kg in the first year of initiating insulin in T2D by different randomized controlled trials and reviews[1,9–11] has been only partly observed in our analysis of real-world observational data.

This might be related to several points: first, in randomized controlled trials, highly selected, predefined, small study populations, including rather younger patients with less severe overweight or obesity, are usually considered that are not necessarily representative for typical patients in clinical care. Discrepancies to real-world settings indicating weaker associations between insulin use and weight gain were thereby previously reported.[12]

Second, subjects with interacting medications (e.g., specific oral antidiabetic drugs and antidepressive medication), bariatric procedures, psychiatric comorbidities, or other severe disorders that have the potential to influence weight were precluded from our analysis. In clinical care, the impression of insulin-related weight gain might be colored by such interactions that overlap with insulin use and are falsely interpreted as weight gain due to insulin.

Nevertheless, there exist a small group of subjects ($\sim$8% in our study) experiencing a tremendous *BMI increase* on average of +4 kg/m^2 at 2 years after initiating insulin that is mainly characterized by younger age at insulin start (≤70 years), BMI below 30 kg/m^2, and worse metabolic control before insulin initiation. Further, higher HbA1c and higher daily insulin dose within the first half-year and the presence of severe hypoglycemic events during insulin therapy were covariates associated with clear *BMI increase*.

This is well in line with previous reports on real-world data indicating an independent prediction of weight gain in T2D by higher insulin dose, a high baseline HbA1c and a low baseline BMI.[13,14] Moreover, the presence and fear of severe hypoglycemia might increase energy intake by irregular snacks containing mainly simple carbohydrates and by inducing hunger, which is often compensated by high-fat, high-calorie, and high-sugar foods that in turn contribute to a higher weight gain during insulin therapy.

The relationship between a low baseline BMI and weight gain may be in contrast to some clinical perceptions of uncontrolled weight gain in patients with severe obesity after insulin initiation. However, even the opposite seems to be true. There exists a group of patients ($\sim$13% in our study) that are able to reduce their BMI despite insulin initiation. Being obese before the start of insulin was related with a higher odd of belonging to the *BMI decreasing* class.

A longitudinal cross-sectional U.S. study categorized 144,857 patients with T2D by their initial BMI level and reported also less body weight increase in subjects with obesity compared to patients with normal-weight or overweight over 2 years of insulin treatment.[14] Subjects with a BMI >40 kg/m^2 even lost weight of up to −2.2 kg.[14] Paul et al. used simple, a priori grouping of patients by their initial BMI and analyzed the BMI change cross-sectionally. By contrast, our statistical GBT approach defines subgroups of patients longitudinally by their individual BMI change after initiating insulin, which is also different to other clustering techniques like k-means.[15]

Altogether, our data and those of previous observational studies[13,14] provide reassurance to caregivers and patients to timely start insulin even if the patient is obese and having weight concerns to prevent long-term diabetes-related complications.

Another factor related to *BMI decrease* commencing insulin seems to be an older age at insulin initiation (>70 years). With increasing age, natural physiological changes like appetite loss, altered sense of taste and smell, also dysphagia, and reduced food diversity and social environmental circumstances are factors increasing the risk for frailty and sarcopenia.[16] Reduced physical activity in the elderly also contributes to reduction in lean body mass. Paired with chronic disorders, weight loss is often common in the elderly and might partially explain our finding. However, similar delta-BMI trajectories could be observed in our age-stratified analysis for patients aged 40 to <50 years at insulin start, with the exception of a higher average *BMI decrease* at 2 years of follow-up in the older age group (≥50 years; Table 2).

Another potential explanation for the *BMI decrease* during insulin therapy, particularly in patients with obesity, might be an increased motivation to maintain or lose weight, which is part of standard counseling in T2D. We regret that we could not control for active participation in conventional weight loss interventions (diet plus exercise) or different lifestyle attempts. With such programs, a BMI reduction of −1.6 kg/m^2 within 1 year has been reported in a meta-analysis.[17]

In addition, in unadjusted comparisons, although not statistically significant, the *BMI decreasing* group used metformin more often. The use of metformin is reported to be weight neutral or even linked with weight reduction in clinical trials.[3] Moreover, there is some clinical evidence that adding metformin to an existing stable insulin regimen might prevent insulin-associated weight gain.[18]

Nearly 80% and thereby the majority of our patients with T2D had only a *slight BMI increase* within the first 2 years of insulin therapy. This contrasts with findings mostly from randomized controlled trials reporting often dramatic BMI/-weight increase after commencing insulin use, especially within the first 3 years.[1,9–11,19]

Large, observational studies on the effect of insulin on BMI/weight are still rare. A part of the observed *slight BMI increase* in our study might be explained by weight loss before insulin therapy[14,19] due to inadequate metabolic control, insulin deficiency, and glycosuria. In a small sample of 58 patients with T2D, Larger et al. observed weight loss before diabetes diagnosis that continued until insulin start.[19] Further, the authors stated that the weight patients gained while using insulin is highly correlated with their maximal weight before diagnosis indicating, at least in part, a physiological control of body weight.[19]

Moreover, BMI fluctuations over time exist. For example for Germany, the Augsburg MONICA (MONItoring of trends and determinants in CArdiovascular disease) surveys report, for the general population, a BMI change over 5 years in the range of +0.1 to +0.7 kg/m^2.[20] In a Canadian study among 3070 middle-aged and elderly people a slight, continuous BMI increase with time of 2.6 kg/m^2 within 10 years was observed.[21]

Commonly, the initial insulin regimen in adult T2D is the BOT, due to simplicity and overall good patient acceptance.[2,3] However, on the long-term, ICT is most common.[3,22] The type of insulin regimen seems to play a role as

simpler insulin regimens with biphasic or premixed insulins were associated with less weight gain compared to basal-prandial insulin regimens in some randomized controlled trials,[23,24] although the results are heterogeneous.[9] Moreover, not all insulin preparations equally affect body weight. For instance, the long-acting insulin analog detemir is linked to lesser weight gain compared to NPH or insulin glargine, with greatest effects in patients with obesity.[9,25]

In our observational data, such associations could only be partly observed. In line with the noninterventional CREDIT study (Cardiovascular Risk Evaluation in people with type 2 Diabetes on Insulin Therapy) that evaluated body weight change after 1 year of any insulin treatment among 2179 patients with T2D from 12 countries, insulin regimen was not a predictive factor in multivariable regression analysis.[13]

A major strength of our large, real-world observational, longitudinal study is that we can provide information on how insulin affects BMI in ''real-life'' instead of head-to-head comparisons between drugs in clinical trials. Nevertheless, the post hoc analysis of electronically recorded health data from routine clinical care sometimes implies several challenges as different interactions on the clinical and also social level are present and data completeness could not be guaranteed.

For example, to not bias the effect of insulin on BMI, we had to exclude patients with other oral antidiabetic medication due to their known effect on weight (either weight loss or weight gain). However, to consider the current treatment recommendations of combining (basal) insulin with oral antidiabetic medication, we included patients using metformin and DPP-4 inhibitors as they are assumed to be nearly weight neutral.[3]

Data on a longer time period and other relevant covariates such as psychiatric comorbidities or diabetes-related distress[9,10] that influence weight are needed to substantiate our results. In real-world settings, the interaction of different covariates (e.g., family situation, socioeconomics, mental health, and drug interactions) may sometimes limit the analysis of the true effect of insulin on BMI change.

Overall, post hoc observational analyses do not provide the same evidence as primary prespecified analyses. For example, observed statistical relationships may indicate cause and effect, but this is misleading, as in post hoc analysis, we cannot say whether the observed finding is a consequence or a cause of the result. Moreover, differences observed between subgroups can be a simple coincidence.

Keeping this in mind, results of post hoc analyses should be interpreted with caution and sufficient justification. However, they can help to generate scientific hypotheses or trends that can be then studied in randomized clinical trials.

Conclusion

Our data from routine clinical care considering individual BMI changes within the first 2 years after initiating insulin could help to close key knowledge gaps and underline that general fear and delay of insulin initiation due to weight concerns is exaggerated, particularly in subjects with obesity before insulin start. The slight insulin-associated BMI increase observed in the majority of subjects might be minimized by structured lifestyle advice.

Nonetheless, clinicians should put a special focus on patients most at risk for BMI increase starting insulin therapy: younger age (<70 years), normal weight or overweight prior insulin initiation, worse metabolic control both prior and during insulin use, as well as the presence of severe hypoglycemic events.

Authors' Contributions

N.P. contributed to conception and design of the study and the statistical analysis, wrote the article draft, and created figures and tables; A.S. contributed to conception and design of the study, performed statistical analysis, reviewed and edited the article, and contributed to interpretation of results; B.B., B.H., H.-P.K., J.K.M., S.M., R.W.-L., and F.-J.W. collected data and reviewed and edited the article; R.W.H. contributed to conception and design of the study, reviewed and edited the article. All authors have given final approval of the version to be published and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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Supplementary Material

Supplementary Figure S1
Supplementary Appendix SA1

References

1. Erpeldinger S, Rehman MB, Berkhout C, et al.: Efficacy and safety of insulin in type 2 diabetes: meta-analysis of randomised controlled trials. BMC Endocr Disord 2016; 16:39.

2. Davies MJ, D'Alessio DA, Fradkin J, et al.: Management of hyperglycaemia in type 2 diabetes, 2018. A consensus report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetologia 2018;61:2461–2498.
3. Bundesärztekammer (BÄK), Kassenärztliche Bundesvereinigung (KBV), Arbeitsgemeinschaft der Wissenschaftlichen Medizinischen Fachgesellschaften (AWMF): [Nationale Versorgungsleitlinie typ-2-diabetes—Langfassung, 2. Auflage. Version 1. 2021] (in English: National Care Guidelines Type2 Diabetes—long edition. 2nd edition. version 1. 2021). DOI: 106101/AZQ/000476 www.leitlinie.de/diabetes (accessed August 16, 2021).
4. Prinz N, Schwandt A, Becker M, et al.: Trajectories of body mass index from childhood to young adulthood among patients with type 1 diabetes-a longitudinal group-based modeling approach based on the DPV registry. J Pediatr 2018;201:78–85.e4.
5. Hofer SE, Schwandt A, Holl RW, Initiative AD: Standardized documentation in pediatric diabetology: experience from Austria and Germany. J Diabetes Sci Technol 2016; 10:1042–1049.
6. Workgroup on Hypoglycemia, American Diabetes Association: Defining and reporting hypoglycemia in diabetes: a report from the American Diabetes Association workgroup on hypoglycemia. Diabetes Care 2005;28:1245–1249.
7. Rosenbauer J, Dost A, Karges B, et al.: Improved metabolic control in children and adolescents with type 1 diabetes: a trend analysis using prospective multicenter data from Germany and Austria. Diabetes Care 2012;35:80–86.
8. Nagin DS: Group-based modeling of development. https://www.hup.harvard.edu/catalog.php?isbn=9780674016866 (accessed August 26, 2020).
9. Brown A, Guess N, Dornhorst A, et al.: Insulin-associated weight gain in obese type 2 diabetes mellitus patients: what can be done? Diabetes Obes Metab 2017;19:1655–1668.
10. Jansen HJ, Vervoort GMM, de Haan AFJ, et al.: Diabetes-related distress, insulin dose, and age contribute to insulin-associated weight gain in patients with type 2 diabetes: results of a prospective study. Diabetes Care 2014;37: 2710–2717.
11. Pontiroli AE, Miele L, Morabito A.: Increase of body weight during the first year of intensive insulin treatment in type 2 diabetes: systematic review and meta-analysis. Diabetes Obes Metab 2011;13:1008–1019.
12. Anyanwagu U, Mamza J, Gordon J, et al.: Premixed vs basal-bolus insulin regimen in type 2 diabetes: comparison of clinical outcomes from randomized controlled trials and real-world data. Diabet Med 2017;34:1728–1736.
13. Balkau B, Home PD, Vincent M, et al.: Factors associated with weight gain in people with type 2 diabetes starting on insulin. Diabetes Care 2014;37:2108–2113.
14. Paul SK, Shaw JE, Montvida O, et al.: 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 2016; 18:1244–1252.
15. Twisk J, Hoekstra T: Classifying developmental trajectories over time should be done with great caution: a comparison between methods. J Clin Epidemiol 2012;65: 1078–1087.
16. Cox NJ, Morrison L, Ibrahim K, et al.: New horizons in appetite and the anorexia of ageing. Age Ageing 2020;49: 526–534.
17. Barte J, Veldwijk J, Teixeira P, et al.: Differences in weight loss across different BMI classes: a meta-analysis of the effects of interventions with diet and exercise. Int J Behav Med 2014;21:784–793.
18. Jacob AN, Salinas K, Adams-Huet B, et al.: Weight gain in type 2 diabetes mellitus. Diabetes Obes Metab 2007;9:386–393.
19. Larger E, Rufat P, Dubois-Laforgue D, et al.: Insulin therapy does not itself induce weight gain in patients with type 2 diabetes. Diabetes Care 2001;24:1849–1850.
20. Liese A, Döring A, Hense H, et al.: Five year changes in waist circumference, body mass index and obesity in Augsburg, Germany. Eur J Nutr 2001;40:282–288.
21. Wang M, Yi Y, Roebothan B, et al.: Body mass index trajectories among middle-aged and elderly Canadians and associated health outcomes. J Environ Public Health 2016; 2016:7014857.
22. Bohn B, Kerner W, Seufert J, et al.: Trend of antihyperglycaemic therapy and glycaemic control in 184,864 adults with type 1 or 2 diabetes between 2002 and 2014: analysis of real-life data from the DPV registry from Germany and Austria. Diabetes Res Clin Pract 2016;115:31–38.
23. Wang C, Mamza J, Idris I: Biphasic vs basal bolus insulin regimen in type 2 diabetes: a systematic review and meta-analysis of randomized controlled trials. Diabet Med 2015; 32:585–594.
24. Holman RR, Farmer AJ, Davies MJ, et al.: Three-year efficacy of complex insulin regimens in type 2 diabetes. N Engl J Med 2009;361:1736–1747.
25. Russell-Jones D, Danne T, Hermansen K, et al.: Weight-sparing effect of insulin detemir: a consequence of central nervous system-mediated reduced energy intake? Diabetes Obes Metab 2015;17:919–927.

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