Weight gain in insulin treated patients by BMI categories at treatment initiation: New evidence from real-world data in patients with type 2 diabetes

Short Title: Weight gain in insulin treated patients by BMI categories

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Abstract

Aims

In type 2 diabetes patients (T2DM) treated with insulin, the aims were to evaluate the extent of weight gain over two years of insulin treatment, and the dynamics of weight gain with glycaemic achievements over time by adiposity levels at insulin initiation.

Materials and Methods

T2DM patients (n=155,917), who commenced insulin therapy and continued it for at least six months were selected from a large USA database of electronic medical records. Longitudinal changes in body weight and HbA1c by BMI categories were estimated.

Results

Patients had a mean age of 59 years, HbA1c 9.5%, and BMI 35 kg/m² at insulin initiation.

The HbA1c levels at insulin initiation were significantly lower (9.2% to 9.4%) in the obese patients, than in patients with normal body weight (10.0%). However, the proportions of patients with HbA1c >7.5% or >8.0% were similar across the BMI categories.

The adjusted weight gain progressively fell with increasing baseline BMI category over 6, 12 and 24 months (p <0.01). The adjusted changes in HbA1c were similar across BMI categories. A 1% decrease in HbA1c was associated with progressively less weight gain as

pre-treatment BMI rose, ranging from a 1.24 kg gain in those with BMI < 25 kg/m² to a 0.32 kg loss in those with BMI > 40 kg/m².

Conclusions

During 24 months of insulin treatment, obese patients gained significantly less body weight compared to normal and overweight patients, while achieving clinically similar glycaemic benefits. These data provide reassurance for the use of insulin in obese patients.

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INTRODUCTION

Type 2 diabetes (T2DM) is a progressive disease in which beta-cell function continues to decline over time, leading to the need for insulin treatment in a significant proportion of patients. Although studies suggest that early initiation of insulin supplementation may alter the progressive course of T2DM, insulin initiation is often delayed mainly due to patients' hesitation and physician barriers [1-7]. This may significantly increase the risk of developing diabetic complications [7, 8]. Fear of weight gain is one of the common reasons for delaying insulin therapy, and concerns about potential weight gain are usually greatest for those who are already obese [9-12].

While many studies have reported significant weight gain associated with insulin therapy, no study, to the best of our knowledge, has explored the weight gain with insulin therapy according to adiposity levels at the time of insulin initiation. If it were the case that insulin-related weight gain declines with increasing pre-treatment adiposity, then significant reassurance could be provided to obese patients, and timely insulin therapy could be initiated.

In this longitudinal study, using data from a comprehensive electronic medical record database, the aims were to evaluate the following, according to pre-treatment BMI categories: (1) the change in body weight over two years post initiation of insulin treatment, (2) the glycaemic control in these patients in relation to weight change, and (3) the weight gain associated with a 1 percentage point improvement in HbA1c.

MATERIALS AND METHODS

Data Source

The General Electronic CentricityTM Electronic Medical Records (CEMR) contains more than 40 million patients' clinical/treatment records from 1995 to January 2015. CEMR represents 49 US states and consists of over 35,000 health care providers, about 70% being primary care providers. CEMR database stores data on medication prescriptions within EMR network, and also information on medications that may be used over the counter or prescribed out of EMR network. This database includes insured and uninsured patients, and has been extensively used for academic research worldwide [13-17].

From more than 1.6 million patients with T2DM, a cohort of 432,287 patients, who received at least one prescription of insulin on or after diagnosis of T2DM, was selected. Identification of T2DM was based on the ICD-9 codes and at least two prescriptions for any anti-diabetes drugs (ADDs) within six months of diagnosis of T2DM. Patients with incomplete description of the disease, and with any record of type 1 diabetes longitudinally were excluded.

Conditions of no missing data on age, sex, ethnicity at diagnosis of T2DM, age at insulin initiation between 18 and 75 years, first prescription date of insulin on or after 1st January 1995, no missing data on body weight and HbA1c on or within three months prior to first date of insulin prescription, and any prescription of GLP-1 receptor agonists (GLP-1 RA) during the follow-up period, were incorporated. The cohort sizes with 6 / 12 / 24 months of insulin treatment duration were 155,917 / 151,220 (Sub-cohort 1) / 144,857 (Sub-cohort 2), respectively.

BMI at insulin initiation was categorised as BMI < 25 kg/ m² (normal weight), BMI ≥ 25 kg/ m² and < 30 kg/ m² (overweight), BMI ≥ 30 kg/ m² and < 35 kg/ m² (Grade 1 obesity), BMI ≥ 35 kg/ m² and < 40 kg/ m² (Grade 2 obesity), and BMI ≥ 40 kg/ m² (Grade 3 obesity).

Baseline data included age, sex, ethnicity, body weight, BMI, and blood pressure at the time of diagnosis of diabetes and at the time of insulin initiation (index date, ID). Longitudinal clinical and laboratory measures were arranged on the basis of 6-monthly windows, progressively from 6 months prior of the index date, and only the latest measurement within each window was preserved. For example, the latest HbA1c value measured >6 months and <12 months of index date was kept as HbA1c at 12 months. Complete information on ADD, anti-hypertensive and cardioprotective medications over time was obtained along with dates of prescriptions. For ADD, information was extracted on any medication that was prescribed post diagnosis of diabetes and post ID. The treatment duration with individual medications were calculated.

Statistical methods

The proportions of patients with missing data on body weight and HbA1c between 6 and 24 months of follow-up ranged between 9% to 16% and 8% to 17% respectively. The missing data were imputed using multiple imputation technique, with adjustments for age at insulin initiation, diabetes duration at insulin initiation and the usages of oral anti-diabetes drugs (OAD) during follow-up. All primary analyses were conducted using the imputed weight and HbA1c data, with additional analyses based on complete cases for sensitivity analyses.

The mean (95% CI) changes in body weight and HbA1c at 6, 12 and 24 months for the main study cohort and the two sub-cohorts were obtained using weighted multivariate regression models, adjusting for age at ID, sex, diabetes duration at ID, OAD usages, and the distribution of weight or HbA1c at ID, separately for BMI categories at ID. The regression models for weight and HbA1c change were weighted by baseline weight and HbA1c

respectively. The mean (95% CI) of possible marginal contribution of sulfonylurea usage on weight and HbA1c changes were estimated using the same regression models, as appropriate. Separate sensitivity analyses were conducted using data from patients with a minimum of two years of diabetes duration at ID, to verify the consistency of the findings on weight change by BMI categories at index date. Additional sensitivity analyses included evaluations of changes in body weight and HbA1c with further adjustments for the insulin regimen at ID, and among those who did not undergo any bariatric surgery procedure prior to insulin initiation or during follow-up (n=153,788).

To evaluate the possible association of a 1% reduction in HbA1c by insulin $\pm$ other anti-diabetes drugs on weight gain over 6, 12 and 24 months of insulin treatment, multivariate factorial regression models were fitted. For example, to evaluate the possible association of 1% reduction in HbA1c at 12 months of treatment, the fitted model was:

$$(weight_{12m} - weight_{ID}) \sim function \{age_{ID} + sex + diabetes\ duration_{ID} + use\ of\ any\ OAD\ on\ ID\ or\ during\ 12\ months\ of\ follow-up + (BMI\ categories\ at\ ID) * (HbA1c_{12m} - HbA1c_{ID})\} \text{ --}$$

weighted by weight_{ID}

The regression based approach described above was also used to evaluate the possible differences in the patterns of association of HbA1c change with weight change in people with different BMI levels at insulin initiation.

RESULTS

The demographic, clinical, laboratory and medications data at the time of insulin initiation are presented in Table 1, for the whole study cohort (n=155,917) and the two sub-cohorts defined on the basis of minimum insulin treatment duration of 12 months (n=151,220) and 24

months (n=144,857). In the whole cohort, patients had a mean (SD) age of 59 (11) years, 48% were male, 54% were White Caucasian, and the median diabetes duration at ID was approximately two years. The mean HbA1c at insulin initiation (9.5%), and the proportions of patients with HbA1c above 7.5% and 8% were similar in all cohorts.

Table 2 shows the baseline characteristics according to BMI categories. Female and White Caucasians were more likely to have higher BMI at ID. The diabetes duration was similar among the BMI groups. The mean HbA1c at ID were significantly lower (9.2% to 9.4%) in the obese patients, compared to patients with normal body weight (10.0%). However, the proportions of patients with HbA1c above 7.5% and 8.0% were similar across the BMI categories. The obese patients were more likely to be on concomitant metformin and/or sulfonylurea therapies compared to patients with normal weight.

Weight change

Weight change over 24 months is presented in Figure 1 and Table 3. The weight gain was significantly and consistently less in patients with higher BMI, compared to that in patients with normal body weight. In Grade 1 and Grade 2 obese patients, the adjusted mean weight gain over 6 and 12 months of insulin treatment ranged between 0.1 kg and 0.9 kg (Table 3), combining the main cohort and sub-cohort 1. In Grade 3 obese patients, the adjusted reductions in body weight were 0.7 kg, 1.1 kg and 2.2 kg over 6, 12 and 24 months of insulin treatment, respectively. The adjusted mean weight gain in the normal weight patients ranged between 2 kg and 4 kg over 6 to 24 months of insulin treatment. In normal weight and overweight patients, the mean weight gain was significantly higher than obese patients. As evident from Figure 1 (C), normal weight and overweight patients continuously gained

weight over two years of follow-up, while a declined body weight trajectories were observed in obese patients after 12 months of insulin initiation in obese patients.

The proportions of patients with 5 kg or more weight gain were significantly lower in obese groups (16% to 19%) compared to normal weight patients (28% to 37%) during 12 and 24 months of insulin treatment (Table 3). Sulfonylurea treatment only marginally contributed to the weight gain (0.17 kg to 0.27 kg over 6 to 24 months of insulin treatment).

About 28% of patients (n=53,879) had a minimum of two years diabetes duration at insulin initiation (Supplementary Table 1). The patterns of weight change by BMI categories in this subset of patients were similar to those observed in all patients across the insulin treatment duration categories. The observed weight change in different BMI categories were similar after adjustments for insulin regimen, and also for those who did not undergo any bariatric procedure(s).

Glycaemic control

The 6-monthly longitudinal measures (mean (95% CI)) of HbA1c over 24 months from ID are presented in Figure 1B. The adjusted changes in HbA1c at 6, 12 and 24 months over the BMI categories are presented in Table 4. Starting with a significantly higher HbA1c of 10% at the ID (compared to overweight and obese patients), the normal weight patients had a mean reduction in HbA1c of about 1.4% over 6 to 24 months of insulin treatment. The overweight, Grade 1 and Grade 2 obese patients had similar glycaemic achievements over the follow-up time (1.0% to 1.3%). Although the HbA1c reduction in Grade 3 obese patients were statistically significantly lower compared to the other groups of overweight and obese patients, these were clinically marginal differences.

In the main study cohort, the proportions of patients on metformin, sulfonylurea or both medications were 70%, 48% and 39% respectively. Among normal weight patients with a minimum of 24 months of insulin treatment (n=13,153 of 144,857), the proportions of patients receiving metformin, sulfonylurea or both were 60%, 41% and 33% respectively. The distributions of usages of these drugs alone or in combination were similar for overweight and obese patients, and were significantly higher compared to the usages observed among the normal weight patients (Table 2). The adjusted marginal HbA1c reduction, associated with metformin treatment, were 0.37%, 0.38% and 0.31% at 6, 12 and 24 months of follow-up. The adjusted changes in HbA1c level associated with sulfonylurea were marginal (Table 4). These estimates were similar across all BMI categories (results are not presented).

Association of weight change with improvement in glycaemic control

The adjusted estimates (regression coefficients) and 95% CIs of weight gain associated with 1% reduction in HbA1c by BMI categories over 6, 12 and 24 months of insulin treatment among patients in sub-cohort 2 are presented in Table 3 and Figure 1D. The estimated weight gains were significantly lower among obese patients compared to the normal and overweight patients. While a 1% HbA1c reduction was associated with weight gains of 0.92 kg and 1.24 kg among normal weight patients at 12 and 24 months of insulin treatment, weight gain was 0.13 kg to 0.46 kg among Grade 1 and Grade 2 obese patients during the same follow-up period. Among Grade 3 obese patients, a 1% HbA1c reduction was not associated with any increase in weight.

Pattern of association of weight change with glycaemic control by BMI categories

Figure 1D shows a difference in the association between HbA1c reduction and weight gain by BMI category. For example, at 24 months of treatment, with the slope (95% CI) of 1.24 (1.18, 1.31) kg associated with 1% reduction in HbA1c for normal weight patients as reference, the differences in the slopes for obese categories (from slope for normal weight category) were significantly different ($p < 0.01$) from zero, and were also significantly different among three obese categories. The differences in the slopes in overweight, Grade 1 and Grade 2 categories were 0.43 kg, 0.78 kg and 1.11 kg respectively ($p < 0.01$). The difference in estimated slopes in the normal weight and Grade 3 obese patients was 1.56 kg. The pattern of association of longitudinal changes in body weight with HbA1c was similar for different ethnic groups.

As a sensitivity analysis, all analyses (described above) were also conducted in patients with complete data on weight and HbA1c measures at 6, 12 and 24 months of follow-up. No difference in the estimates or inferences was observed between complete case analyses and analyses based on the imputed data.

DISCUSSION

This exploratory clinical study, based on large longitudinal real world data, clearly suggests that (1) weight gain associated with insulin treatment is significantly lower in obese patients with T2DM, compared to that observed in patients with normal body weight, (2) the significantly less weight gain in obese patients is consistent over 6, 12 and 24 months of treatment with insulin, adjusted for various factors including the use of concomitant anti-diabetes medications, (3) the glycaemic control over 24 months of treatment with insulin is

similar among patients with different BMI levels, and (4) the weight gain associated with a 1% reduction in HbA1c falls progressively, as pre-treatment BMI increases.

Our finding that obese patients gain significantly less weight with insulin treatment is robust, and is supported by consistent estimates of weight changes by different BMI categories over 6 to 24 months of insulin treatment (Figure 1C). Separate analyses to explore possible confounders, through evaluation of various characteristics by BMI categories in patients with a minimum of two years of treatment with insulin (Table 2), provide a basis to support this robust finding. This is further supported by consistent findings in patients with a minimum of two years of diabetes duration before insulin initiation (Supplementary Table 1). It is likely that some of the normal weight patients ($\text{BMI} < 25 \text{ kg/m}^2$), and perhaps some with BMI 25-30 kg/m^2 had lost weight prior to commencing insulin, which may account for some of their weight gain post insulin initiation. However, we still see progressive reductions in body weight gain with progressive increases in baseline BMI above 30 kg/m^2 .

The level of HbA1c reached over time was clinically similar in the different BMI groups, despite the fact that obese patients had significantly lower HbA1c levels (9.2% to 9.4%) at insulin initiation compared to those with normal body weight or overweight (9.7% to 10.0%, Table 2). Thus, patients arrive at approximately the same HbA1c level, independent of the starting value. This might suggest that the lesser weight gain seen in obese patients was due to the use of less intensive insulin therapy. Although we did not have insulin dose data, we nevertheless showed that even when corrected for the same HbA1c reduction, weight gain remained smaller in the obese group.

Based on a cohort of 2,179 patients with about nine years of median diabetes duration, Balkau and colleagues reported 1.78 kg of average weight gain (unadjusted) over one year of treatment with insulin, with 24% patients experiencing ≥ 5 kg of weight gain, and a significant inverse association of baseline BMI with weight gain [18]. The adjusted mean weight gain in our study cohort with a minimum of one year of treatment with insulin (Cohort 2) ranged between 0.2 kg and 3.49 kg among patients with BMI ≤ 40 kg/m² (combining sub-cohorts 1 and 2). A marginal weight loss was observed in patients with Grade 3 obesity. The proportion of patients gaining 5 kg or more body weight at one year was similar across obese patients (16% to 17%, Table 3), while 28% of patients with normal body weight gained 5 kg or more. Compared to normal weight, patients in grade 1, 2 and 3 obesity category were 48%, 51% and 50% less likely to increase body weight above 5 kg.

We observed that the cost of glycaemic control in terms of weight gain is marginal in Grade 1 and Grade 2 obese patients. Among the Grade 3 obese patients, a 1% reduction in HbA1c was associated with a decrease in weight of about 0.3 kg after 24 months of insulin treatment. Balkau and colleagues reported that a high baseline HbA1c level, insulin dose requirements and lower baseline BMI were independently associated with greater weight gain [18]. From a meta-analysis, Pontiroli and colleagues found that the intensity of treatment, dose of insulin, final HbA1c, change of HbA1c and frequency of hypoglycaemia were significantly associated with weight increase as well as type of insulin regimen [10]. However, these studies did not evaluate the possible association of glycaemic control with weight change in patients with different levels of adiposity at the time of insulin initiation. Our study also

provides new information on the significant differences in the patterns of possible association between glycaemic control and weight change in insulin treated patients by BMI categories.

Electronic databases present challenges in terms of accuracy and completeness of the required data. The limitations of this study include non-availability of complete and reliable data on: (1) medication adherence; (2) diet and exercise; (3) socio-economic status; and (4) potential residual confounders. We believe the non-availability of longitudinal insulin doses would not affect the robustness of our findings, as the main interest was to evaluate the observed weight change and glycaemic control at population level – reflecting the primary/ambulatory care disease risk factor management. Our analysis of weight change in relation to change in HbA1c confirms that the weight gain ‘cost’ of achieving any given improvement in glycaemic control is, in fact, less with increasing pre-treatment BMI.

Although we excluded patients treated with GLP-1 receptor agonists, it is not possible to know to what extent the lesser weight gain with increasing BMI is due to pharmacological differences of the effects of insulin or to other attempts to lose weight in the obese groups. Patients may well intensify lifestyle efforts on commencing insulin. Whether or not this happens more in the more obese is difficult to ascertain because of the non-availability of longitudinal lifestyle intervention data. Thus, these results should not be interpreted as indicating that lifestyle efforts to control weight gain are not necessary for obese patients initiating insulin. Nevertheless, they do indicate that within the facilities available in routine care, weight gain can readily be limited when initiating insulin therapy in obese patients with T2DM.

Large analysis cohort from the validated CEMR database should be considered as a representative sample, and as such, provides a good picture of the state of weight and glycaemic control in routine practice. We had complete data on weight and HbA1c measured within three months of insulin initiation, and the 6-monthly follow-up measures of weight and HbA1c were imputed for only 8% to 16% missing cases. The results from complete case analyses and imputed data were very similar. Finally, careful new-user design with sensible exposure time of two years, and appropriate adjustments for various aspects are the primary strengths of the study.

In conclusion, we observed that over 24 months of treatment with insulin, obese patients gained significantly less weight compared to normal and overweight patients, while achieving clinically similar glycaemic benefits. These findings should provide important reassurance that, among obese patients with T2DM in routine clinical practice, meaningful improvements in glycaemic control can be achieved with only small increases in weight.

Acknowledgements

SKP conceived the idea and was responsible for the primary design of the study. JS and KK significantly contributed in the study design. KK conducted the data extraction, and SKP, OM and KK jointly conducted the statistical analyses. The first draft of the manuscript was developed by SKP, and all authors contributed to the finalisation of the manuscript. SKP had full access to all the data in the study and is the guarantor, taking responsibility for the integrity of the data and the accuracy of the data analysis.

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Conflict of Interest

SKP has acted as a consultant and/or speaker for Novartis, GI Dynamics, Roche, AstraZeneca, Guangzhou Zhongyi Pharmaceutical and Amylin Pharmaceuticals LLC. He has received grants in support of investigator and investigator initiated clinical studies from Merck, Novo Nordisk, AstraZeneca, Hospira, Amylin Pharmaceuticals, Sanofi-Aventis and Pfizer. JS has received honoraria for consultancies and lectures from: Novartis, Novo Nordisk, Astra Zeneca, Sanofi, Merck Sharp and Dohme, Abbott, Janssen Cilag, and Takeda. OM and KK has no conflict of interest to declare.

Transparency Declaration

The lead author (SKP) affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

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Figure Legend

Figure 1: (A) Mean (95% CI) of longitudinal measures of body weight (Kg) over two years from the time of insulin initiation by BMI category at index date; (B) Mean (95% CI) of longitudinal measures of HbA1c over two years from the time of insulin initiation by BMI category at index date; (C) Adjusted mean (95% CI) of change in body weight at 6, 12 and 24 months of treatment with insulin by BMI category at index date; (D) Adjusted mean (95% CI) change in body weight at 6, 12 and 24 months of treatment with insulin, associated with 1% reduction in HbA1c at these time points.

Table 1: Baseline characteristics of main cohort and two sub-cohorts.

	Insulin Treatment e 6 months Main Cohort	Insulin Treatment e 12 months Sub-cohort 1	Insulin Treatment e 12 months Sub-cohort 2
N	155917	151220	144857
Male, n (%)	75,038 (48)	72,797 (48)	69,788 (48)
Ethnicity, n (%)			
White Caucasian	83,441 (54)	80,840 (54)	77,431 (54)
Black	21,658 (14)	21,086 (14)	20,274 (14)
Hispanic	6,180 (4)	6,004 (4)	5,740 (4)
Asian	2,789 (2)	2,713 (2)	2,616 (2)
Other/ Unknown	41,489 (27)	40,577 (27)	38,796 (27)
Age at insulin initiation (yr), mean (sd)	59 (11)	59 (11)	59 (11)
Diabetes Duration (yr)			
Median (Q1, Q3)	1.9 (0.2, 2.6)	1.9 (0.2, 2.6)	2.0 (0.2, 2.7)
< two years, n (%)	102,038 (72)	98,911 (72)	94,655 (71)
2 – 5 years, n (%)	25,754 (18)	25,020 (18)	24,027 (18)
> 5 years, n (%)	14,848 (10)	14,431 (10)	13,856 (11)
Weight (kg), mean (sd)	98.8 (26.0)	98.6 (26.0)	98.6 (25.9)
BMI (kg/m²), mean (sd)	34.8 (8.4)	34.8 (8.5)	34.8 (8.4)
BMI Categories*, n (%)			
< 25 kg/m ²	13,880 (9)	13,585 (9)	13,153 (9)
e 25 and < 30 kg/m ²	32,047 (21)	31,254 (21)	30,106 (21)
e 30 and < 35 kg/m ²	43,274 (28)	41,916 (28)	40,153 (28)
e 35 and < 40 kg/m ²	32,445 (21)	31,385 (21)	29,940 (21)

e 40 kg/m ²	34,271 (22)	33,080 (22)	31,505 (22)
HbA1c (%)			
Mean (sd)	9.5 (2.3)	9.5 (2.3)	9.5 (2.2)
Median (Q1, Q3)	9.2 (7.7, 11.0)	9.2 (7.7, 10.9)	9.2 (7.7, 10.9)
HbA1c e 7.5%, n (%)	123,802 (79)	120,111 (79)	114,965 (79)
HbA1c e 8%, n (%)	111,368 (71)	108,052 (72)	103,379 (71)
Anti-Diabetes Medication, n (%)			
Metformin	108,377 (70)	105,084 (70)	100,531 (69)
Sulfonylurea	74,492 (48)	72,305 (48)	69,214 (48)
Insulin Type at Initiation, n (%)			
Basal	99299 (65)	96343 (65)	92212 (65)
Biphasic	21136 (14)	20548 (14)	19843 (14)
Prandial	31314 (21)	30335 (21)	29044 (21)

*The BMI at insulin initiation was categorised as BMI < 25 kg/ m² (normal weight), BMI e 25 kg/ m² and < 30 kg/ m² (overweight), BMI e 30 kg/ m² and < 35 kg/ m² (Grade 1 obesity), BMI e 35 kg/ m² and < 40 kg/ m² (Grade 2 obesity), and BMI e 40 kg/ m² (Grade 3 obesity).

Table 2: Characteristics of study parameters and concomitant medication usage at insulin initiation by BMI categories in patients with minimum 24 months of insulin treatment (Sub-cohort 2).

	BMI Categories				
	< 25 kg/m ²	≥ 25 and < 30 kg/m ²	≥ 30 and < 35 kg/m ²	≥ 35 and < 40 kg/m ²	≥ 40 kg/m ²
N	13,153	30,106	40,153	29,940	31,505
Male, n (%)	7,126 (54)	16,925 (56)	20,847 (52)	13,592 (45)	11,298 (36)
Ethnicity, n (%)					
White Caucasian	6,200 (47)	14,959 (50)	21,491 (54)	16,727 (56)	18,054 (57)
Black	1,851 (14)	4,244 (14)	5,414 (14)	3,967 (13)	4,798 (15)
Hispanic	584 (4)	1,577 (5)	1,641 (4)	1,051 (4)	887 (3)
Asian	639 (5)	891 (3)	603 (2)	267 (1)	216 (1)
Other/ Unknown	3,879 (30)	8,435 (28)	11,004 (28)	7,928 (27)	7,550 (24)
Age at insulin initiation (yr), mean (sd)	58 (12)	60 (11)	59 (11)	59 (11)	57 (12)
Diabetes Duration (yr)					
Median (Q1, Q3)	1.6 (0.1, 1.9)	1.8 (0.1, 2.4)	1.9 (0.1, 2.4)	1.8 (0.1, 2.5)	1.8 (0.1, 2.5)
< two years, n (%)	9,223 (76)	19,800 (71)	26,050 (71)	19,281 (71)	20,301 (71)
2 – 5 years, n (%)	1,927 (16)	5,004 (18)	6,697 (18)	5,076 (19)	5,323 (19)
> 5 years, n (%)	1,015 (8)	2,952 (11)	3,937 (11)	2,892 (11)	3,060 (11)
Weight (kg), n (%)	64.4 (10.5)	79.8 (11.1)	93.8 (13.9)	106.4 (15.0)	130.2 (23.1)
BMI (kg/m²), n (%)	22.5 (2.2)	27.7 (1.4)	32.6 (1.4)	37.3 (1.4)	46.8 (6.9)
HbA1c (%)					

Mean (sd)	10.0 (2.8)	9.7 (2.4)	9.4 (2.3)	9.3 (2.2)	9.2 (2.1)
Median (Q1, Q3)	9.6 (7.7, 12.0)	9.4 (7.8, 11.3)	9.2 (7.7, 10.9)	9.0 (7.7, 10.7)	9.0 (7.6, 10.5)
HbA1c < 7.5%, n (%)	10,400 (79)	24,289 (81)	32,015 (80)	23,686 (79)	24,575 (78)
HbA1c < 8%, n (%)	9,462 (72)	22,045 (73)	28,766 (72)	21,188 (71)	21,918 (70)
Anti-Diabetes Medication, n (%)					
Metformin only	7,892 (60)	20,685 (69)	27,973 (70)	21,328 (71)	22,653 (72)
Sulfonylurea only	5,416 (41)	14,339 (48)	19,378 (48)	14,683 (49)	15,398 (49)
Metformin + Sulfonylurea	4,390 (33)	11,896 (40)	15,945 (40)	12,074 (40)	12,636 (40)
Insulin Type at Initiation, n (%)					
Basal	8164 (64)	19503 (66)	25757 (66)	19018 (65)	19770 (64)
Biphasic	1756 (14)	4114 (14)	5449 (14)	4125 (14)	4399 (14)
Prandial	2901 (23)	5755 (20)	7847 (20)	6025 (21)	6516 (21)

Table 3: Adjusted weight change over 24 months of insulin treatment initiation, by baseline BMI category.

	Main Cohort n=155,917	Sub-cohort 1 n=151,220	Sub-cohort 2 n=144,857	
	Mean (95% CI) weight change*, kg			Mean (95% CI) weight change associated with a 1% reduction in HbA1c [‡]
At 6 months				
BMI < 25 kg/m ²	2.0 (2.0, 2.1)	2.0 (2.0, 2.1)	2.0 (2.0, 2.1)	0.66 (0.61, 0.70)
BMI ≥ 25 and < 30 kg/m ²	1.2 (1.1, 1.2)	1.2 (1.1, 1.2)	1.1 (1.1, 1.2)	0.44 (0.41, 0.47)
BMI ≥ 30 and < 35 kg/m ²	0.6 (0.6, 0.7)	0.6 (0.6, 0.7)	0.6 (0.6, 0.7)	0.29 (0.26, 0.31)
BMI ≥ 35 and < 40 kg/m ²	0.1 (0.1, 0.2)	0.1 (0.1, 0.2)	0.1 (0.1, 0.2)	0.11 (0.08, 0.15)
BMI ≥ 40 kg/m ²	-0.7 (-0.7, -0.6)	-0.7 (-0.7, -0.6)	-0.7 (-0.7, -0.6)	-0.06 (-0.02, 0.0)
At 12 Months				
BMI < 25 kg/m ²	-	3.0 (3.0, 3.1)	3.0 (3.0, 3.1)	0.92 (0.86, 0.97)
BMI ≥ 25 and < 30 kg/m ²	-	1.8 (1.7, 1.8)	1.7 (1.7, 1.8)	0.61 (0.58, 0.65)
BMI ≥ 30 and < 35 kg/m ²	-	0.9 (0.9, 1.0)	0.9 (0.9, 1.0)	0.39 (0.36, 0.43)
BMI ≥ 35 and < 40 kg/m ²	-	0.2 (0.2, 0.3)	0.2 (0.2, 0.3)	0.15 (0.11, 0.19)
BMI ≥ 40 kg/m ²	-	-1.1 (-1.2, -1.1)	-1.1 (-1.2, -1.1)	-0.18 (-0.22, -0.14)
At 24 Month				

BMI < 25 kg/m ²	-	-	3.9 (3.8, 3.9)	1.24 (1.18, 1.31)
BMI e 25 and < 30 kg/m ²	-	-	2.0 (1.9, 2.0)	0.81 (0.76, 0.85)
BMI e 30 and < 35 kg/m ²	-	-	0.7 (0.7, 0.8)	0.46 (0.41, 0.50)
BMI e 35 and < 40 kg/m ²	-	-	-0.2 (-0.3, -0.2)	0.13 (0.08, 0.18)
BMI e 40 kg/m ²	-	-	-2.2 (-2.2, -2.1)	-0.32 (-0.37, -0.27)
Percentage of patients who increased body weight e 5 Kg				
BMI < 25 kg/m ²	13	28	37	-
BMI e 25 and < 30 kg/m ²	12	19	24	-
BMI e 30 and < 35 kg/m ²	11	17	19	-
BMI e 35 and < 40 kg/m ²	11	16	18	-
BMI e 40 kg/m ²	11	17	18	-
Mean (95% CI) of marginal contribution towards changes in weight, kg				
Sulfonylurea treatment	0.17 (0.11, 0.22)	0.25 (0.17, 0.32)	0.27 (0.18, 0.36)	-

*Adjusted for sex, diabetes duration, and metformin and sulfonylurea usage, according to BMI categories at insulin initiation.

†Adjusted for sex, diabetes duration, concomitant anti-diabetic medications usage, and baseline HbA1c, according to BMI categories at insulin initiation. The BMI at insulin initiation was categorised as BMI < 25 kg/ m² (normal weight), BMI e 25 kg/ m² and < 30 kg/ m² (overweight), BMI e 30 kg/ m² and < 35 kg/ m² (Grade 1 obesity), BMI e 35 kg/ m² and < 40 kg/ m² (Grade 2 obesity), and BMI e 40 kg/ m² (Grade 3 obesity).

Table 4: Adjusted HbA1c change over 24 months of insulin treatment initiation, by baseline BMI category.

	Main Cohort n=155,917	Sub-cohort 1 n=151,220	Sub-cohort 2 n=144,857
Mean (95% CI) HbA1c change (%)*			
At 6 months			
< 25 kg/m ²	-1.4 (-1.4, -1.3)	-1.4 (-1.4, -1.3)	-1.3 (-1.3, -1.2)
e 25 and < 30 kg/m ²	-1.3 (-1.3, -1.2)	-1.3 (-1.3, -1.2)	-1.2 (-1.2, -1.1)
e 30 and < 35 kg/m ²	-1.1 (-1.2, -1.1)	-1.1 (-1.2, -1.1)	-1.1 (-1.2, -1.1)
e 35 and < 40 kg/m ²	-1.1 (-1.2, -1.1)	-1.1 (-1.1, -1.0)	-1.1 (-1.1, -1.0)
e 40 kg/m ²	-1.0 (-1.0, -0.9)	-1.0 (-1.0, -0.9)	-1.0 (-1.0, -0.9)
At 12 Months			
< 25 kg/m ²	-	-1.3 (-1.4, -1.3)	-1.3 (-1.3, -1.2)
e 25 and < 30 kg/m ²	-	-1.2 (-1.2, -1.1)	-1.2 (-1.2, -1.1)
e 30 and < 35 kg/m ²	-	-1.1 (-1.1, -1.0)	-1.1 (-1.1, -1.0)
e 35 and < 40 kg/m ²	-	-1.0 (-1.0, -0.9)	-1.0 (-1.1, -1.0)
e 40 kg/m ²	-	-1.0 (-0.1, -0.9)	-1.0 (-1.0, -0.9)
At 24 Month			
< 25 kg/m ²	-	-	-1.4 (-1.4, -1.3)
e 25 and < 30 kg/m ²	-	-	-1.2 (-1.2, -1.1)
e 30 and < 35 kg/m ²	-	-	-1.1 (-1.1, -1.0)
e 35 and < 40 kg/m ²	-	-	-1.0 (-1.1, -1.0)
e 40 kg/m ²	-	-	-1.0 (-1.0, -0.9)
Metformin Treatment			
Yes	-1.2 (-1.3, -1.2)	-1.2 (-1.3, -1.2)	-1.2 (-1.2, -1.1)
No	-0.9 (-0.9, -0.8)	-0.9 (-0.9, -0.8)	-0.9 (-0.9, -0.8)

Mean (95% CI) of marginal contribution towards changes in HbA1c, %			
Sulfonylurea treatment	0.03 (0.02, 0.03)	0.3 (0.1, 0.5)	0.7 (0.5, 0.9)

*Adjusted for sex, diabetes duration, and metformin and sulfonylurea usage. Estimates are provided by BMI categories at insulin initiation. The BMI at insulin initiation was categorised as BMI < 25 kg/ m² (normal weight), BMI ≥ 25 kg/ m² and < 30 kg/ m² (overweight), BMI ≥ 30 kg/ m² and < 35 kg/ m² (Grade 1 obesity), BMI ≥ 35 kg/ m² and < 40 kg/ m² (Grade 2 obesity), and BMI ≥ 40 kg/ m² (Grade 3 obesity).

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