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Prescribed Total Daily Insulin Dose and Predictors of Insulin Dose for Adults with Type 2 Diabetes on Multiple Daily Injections of Insulin: A Retrospective Cohort Study †

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Abstract: Background/Objectives: Limited evidence is available regarding insulin total daily dose (TDD), or the factors associated with TDD, among adults with type 2 diabetes (T2D) using multiple daily injections of insulin (MDI). Our aim was to determine the percentage of adults in the United States (US) with T2D who are prescribed MDI, their prescribed insulin TDD, and potential factors associated with TDD. **Methods**: This retrospective cohort study used deidentified data from the US IQVIA ambulatory electronic medical record database to study adults (≥18 years) with T2D initiating MDI (≥3 daily basal-plus-prandial insulin injections) from 1 January 2017 to 1 July 2022. The TDD was calculated from first evidence of MDI (index date). We used a generalized linear model regression analysis to model the relationship between TDD and clinically relevant factors associated with TDD. **Results**: During the study period, of 3,339,663 adults with T2D, 451,769 (13.5%) had ≥1 basal insulin prescriptions, 206,000 (6.2%) had both basal and prandial insulin prescriptions, and 41,215 (1.2%) were prescribed MDI (mean age, 58 years; 52% women; 62% White/Caucasian, 14% African American; mean body mass index [BMI], 34 kg/m^2). Mean TDD was 96 units (1.0 units/kg/day); median TDD was 80 units (interquartile range, 54–124). In the regression analysis (model R^2, 0.14), factors predicting lower TDD included female sex, African American race, and prior 6-month (pre-index) prescriptions of sulfonylurea, metformin, or 2–3 noninsulin glucose-lowering medications. Predictors of greater TDD included increasing BMI, age 30–64 years, and pre-index SGLT2 inhibitor or GLP-1 RA prescription. **Conclusions**: Among US adults with T2D, 1.2% were prescribed MDI, with a wide range of TDD and median TDD of 80 units. Further research in other populations and using other data sources is warranted to explore prescribed insulin TDD for T2D and to examine other potentially relevant predictors of TDD.

Keywords: cohort study; insulin total daily dose; multiple daily injections; predictors of total daily dose; type 2 diabetes

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1. Introduction

Many individuals with type 2 diabetes (T2D) eventually require insulin to achieve glycemic goals [1]. In the United States (US), an estimated 28% of adults with diabetes used insulin in 2013–2020 [2]; and most of these individuals had T2D [2,3]. The usual progression of treatment intensification for people with T2D is the addition of basal insulin to noninsulin glucose-lowering agents, followed by a basal-plus-prandial (mealtime) insulin regimen requiring multiple daily injections (MDI) [1,4].

The most recent American Diabetes Association (ADA) guidance recommends a starting dose of basal insulin at 0.1–0.2 units/kg/day and adding mealtime insulin as needed to meet glycemic goals [1]. People with T2D are usually more insulin resistant than those with type 1 diabetes (T1D) and require higher total daily insulin doses (TDD) [1,5]. However, adherence to and persistence with insulin therapy in T2D is often poor [6–8], and many people with T2D using insulin or MDI do not achieve glycemic goals [8–11]. By one estimate, among people with commercial insurance in the US, only 15% of people with T2D using MDI achieved an A1C level of <7%, while 40% had an A1C level of ≥9% [9].

With the prevalence of diabetes projected to continue growing both in the US and globally, with concomitant increases in people requiring insulin [3,12–14], there is a need for information about insulin therapy as currently prescribed in T2D. The expanding options provided by newer diabetes technologies, such as automated insulin delivery systems and continuous glucose monitoring (CGM), could potentially facilitate and simplify insulin administration and glucose monitoring for the people with T2D who experience challenges in using MDI [15]. However, limited evidence is available regarding insulin TDD, or the factors associated with TDD, among adults with T2D using MDI.

We sought to understand real-world insulin prescribing for people with T2D using MDI. The objectives of this retrospective observational study were to estimate the percentage of US adults with T2D prescribed MDI (≥3 daily basal and prandial insulin injections), to characterize these individuals and their prescribed TDD, and to evaluate potential factors associated with TDD.

2. Materials and Methods

2.1. Data Source

This retrospective cohort study used deidentified data from the IQVIA ambulatory electronic medical record (aEMR) database, which at the time of the study (1 January 2017 to 1 July 2022) contained approximately 87 million patient records from 100,000 physicians in large practices and physician networks, including both commercially insured and Medicare patients, throughout the US [16]. In addition to patient demographic and clinical information, the IQVIA aEMR database captures medications as prescribed, including strength, form, quantity, frequency, days supplied, and refills. The clinical information includes physical examination findings, comorbidities, laboratory tests and results (including A1C), diagnoses, medical procedures, and other treatments.

The use of deidentified data from the IQVIA aEMR database is compliant with the standards of the US Health Insurance Portability and Accountability Act of 1996 (HIPAA) [17]. This noninterventional study was considered to be exempt from institutional review board approval because it was a retrospective analysis of deidentified data.

2.2. Eligibility Criteria and Study Design

Adults (≥18 years old on 1 January 2017) with a diagnosis of T2D (International Classification of Diseases, Ninth Revision, Clinical Modification [ICD-9-CM] code: 250.x0, 250.x2 or ICD-10-CM code: E11.x) initiating MDI (as defined below) from 1 January 2017 to 1 July 2022 were eligible for the study. Included individuals had to have at least one

valid prescription for basal insulin and at least one valid prescription for prandial insulin with information available for dose and frequency of administration during those 5.5 years, which facilitated the estimation of TDD. Dose information was not considered in the TDD calculations if it was recorded "as needed" (PRN), as carbohydrate units, for pumps, for infusions, or as a sliding scale or coverage scale. Patients with T1D (ICD-9-CM codes 250.x1 or 250.x3 or ICD-10-CM code E10.x) recorded during the study period were excluded, as were those who received U-500 or premixed insulin during the study period. National drug codes (NDCs) were used to identify prescriptions for commonly used insulin types [18].

We identified the index date for each individual as the date of MDI initiation, namely, the date of the first prandial insulin prescription in the data together with the closest basal insulin prescription during the study period when the combined number of valid daily insulin injections was three or more. The pre-index period was defined as 180 days (6 months) before the index date, designated to gather data on demographics and clinical characteristics, including pre-index noninsulin glucose-lowering agents. The post-index period was defined as the time period from the index date until the date of the last insulin prescription during the study period.

2.3. Determination of Total Daily Dose of Insulin

The insulin TDD values for each person and overall (for the study population) were calculated using summary statistics by calendar year and for the period after MDI initiation (post-index period). For example, individual calendar year mean TDD values were calculated as the mean dose for all basal insulin prescriptions during each calendar year summed with the mean dose for all prandial insulin prescriptions during that calendar year, with calculations stopped at the last prescription. If the basal insulin prescription was missing in any calendar year, then the mean basal insulin dose from the previous calendar year was used. Likewise, if the prandial insulin prescription was missing in any calendar year, then the mean of all prandial insulin prescriptions from the previous calendar year was used. The mean TDD for each individual's post-index period was calculated as the sum of TDDs for each calendar year divided by the number of calendar years. In the initial analyses, the minimum and maximum individual mean TDD values of 4 units and 2775 units were considered clinically questionable and likely the result of coding errors; therefore, we elected to exclude the top and bottom 1% of TDD values.

For the full study population, the mean TDD was calculated for each calendar year as the sum of all individual mean TDD values within that calendar year divided by the number of individuals who had TDD values within that year. The maximum TDD for each calendar year was identified by first finding the maximum TDD for each person and then determining the mean of these maximum values for each year among all individuals that year. A parallel approach was conducted to calculate the minimum TDD for each year using the minimum TDD for each person. The mean, maximum, and minimum TDDs during the post-index period were calculated similarly: namely, as the sum of all individual TDD values within the post-index period divided by the number of individuals and as the mean, mean maximum, and mean minimum TDD for the overall post-index period among all people, respectively. We also calculated the median TDD for each year and overall.

2.4. Statistical Analyses

Demographic and clinical characteristics of the study population and outcome measures were described using summary statistics. We also summarized the study population characteristics by insulin quartile, calculated using the TDD for the overall post-index period. Comorbidities were captured using ICD-10 codes, and health status was deter-

mined for each person using the Charlson comorbidity index (CCI), as described by Quan et al. [19].

In addition to descriptive analyses, we used a generalized linear model (GLM) regression analysis to investigate the association of demographic characteristics and pre-index diabetes medications (other than insulin) with insulin TDD (total dose), which was calculated at the index date. Predictor variables were selected based on clinical relevance and included sex, age category, race, US Census Region [20], body mass index (BMI), CCI, noninsulin medications prescribed in the 6-month period before MDI initiation (pre-index period), and number of pre-index noninsulin medications. Four noninsulin medications—glucagon-like peptide 1 receptor agonists (GLP-1 RAs), sodium-glucose cotransporter 2 (SGLT2) inhibitors, metformin, and sulfonylureas—were included as binary variables (yes/no) according to whether a prescription record was identified in the pre-index period. In addition, we included binary variables representing the number of concomitant noninsulin medications (1, 2, $\geq$3 vs. none) recorded in addition to insulin during the pre-index period.

The GLM regressions were implemented using standard linear regression, with a log-link function to model the relationships. A gamma distribution was specified given that TDD is positive and continuous, and the mean TDD histogram indicated that the data were right-skewed. A log-link function was employed to improve model fit by normalizing the relationships between predictors and the TDD. All variables were included in the model. Nearly all variables were found to be statistically significant at a 5% level, and the remaining variables were retained, given support from the theory of connection.

Statistical analyses were conducted using SAS software, version 9.4 (SAS Institute, Cary, NC, USA).

3. Results

3.1. Study Population

We identified 3,339,663 individuals in the IQVIA dataset who were 18 years or older at the start of the study period and who had at least one recorded diagnosis of T2D, with no recorded diagnosis of T1D (Figure 1). Of these individuals, 520,847 had at least one prescription of basal or prandial insulin recorded from 1 January 2017 to 1 July 2022, and 41,926 of 520,847 were prescribed MDI and had available dose and frequency information for at least one prandial insulin prescription. After excluding people prescribed the top and bottom 1% of the mean TDD (details provided in Methods), 41,215 people were included in the study (Figure 1). Overall, during the study period, of the 3,339,663 adults in the dataset with T2D, 13.5% (n = 451,769) had one or more basal insulin prescriptions, 6.2% (n = 206,000) had both basal and prandial insulin prescriptions, and 1.2% (n = 41,215) were prescribed MDI (Supplemental Table S1).

Women comprised 52% of the study population, and, overall, mean age was 58 years (SD, 13 years), with one-third (34%) of the study population 65 years or older (Table 1). The majority (62%) were of White/Caucasian race, 14% were African American, and 2% were Asian individuals; 22% of people were of other races or had no recorded race. Approximately half (48%) of people lived in the South, and the lowest percentage (13%) lived in the Northeast Census Region [20]. Renal disease was the most common comorbidity (22%), followed by pulmonary diseases (18%).

From TDD quartile 1 to quartile 4, the mean TDD increased from 0.4 units/kg (quartile 1) to 1.6 units/kg (quartile 4), the mean weight increased from 87.5 kg to 109.7 kg, while the mean BMI increased from 31.0 kg/m^2 to 37.0 kg/m^2 (Table 1). The percentage of women across insulin quartiles was similar (50% to 53%), while the percentage of people $\geq$65 years of age decreased from insulin quartile 1 (41%) to quartile 4 (27%). Over half of African

American (57%) and Asian (60%) individuals were in quartile 1 or 2, while slightly over half (52%) of White/Caucasian individuals were in quartiles 3 or 4.

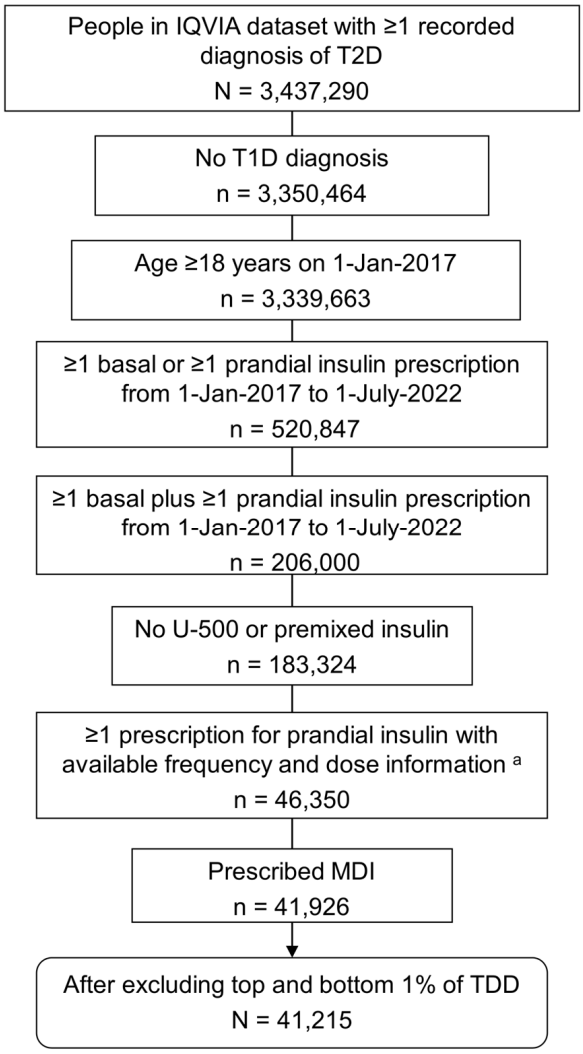

Figure 1. The identification of the study population with type 2 diabetes prescribed multiple daily injections of insulin. [a] Available prandial insulin dose and frequency was found in Signa_txt, a structured free text data field found within the IQVIA dataset. MDI, multiple daily injections of insulin; TDD, total daily dose of insulin; T1D/T2D, type 1/type 2 diabetes.

Table 1. Demographics and clinical characteristics of the overall study population and by insulin total daily dose quartiles.

Variable	Overall N = 41,215	Insulin Total Daily Dose (TDD) Quartile			
		Quartile 1 ***n*** **= 10,312**	**Quartile 2** ***n*** **= 10,358**	**Quartile 3** ***n*** **= 10,283**	**Quartile 4** ***n*** **= 10,262**
TDD/kg, mean (SD), units/kg	1.0 (2.3)	0.4 (0.4)	0.7 (0.3)	1.0 (0.5)	1.6 (1.9)
TDD, mean (SD), units	95.9 (58.1)	38.7 (9.2)	66.8 (8.0)	100.5 (12.2)	178.4 (47.8)
Female sex, *n* (%)	21,481 (52.1)	5422 (52.6)	5449 (52.6)	5436 (52.9)	5174 (50.4)
Age, mean (SD)	57.8 (13.3)	59.6 (14.2)	57.9 (13.6)	57.4 (12.9)	56.4 (12.1)
Age group, *n* (%)					
18–34	2429 (5.9)	643 (6.2)	647 (6.3)	596 (5.8)	543 (5.3)
35–44	4259 (10.3)	955 (9.3)	1065 (10.3)	1072 (10.4)	1167 (11.4)
45–54	8471 (20.6)	1747 (16.9)	2135 (20.6)	2148 (20.9)	2441 (23.8)
55–64	12,219 (29.7)	2716 (26.3)	2914 (28.1)	3238 (31.5)	3351 (32.7)
≥65	13,837 (33.6)	4251 (41.2)	3597 (34.7)	3229 (31.4)	2760 (26.9)

Table 1. *Cont.*

Variable	Overall N = 41,215	Insulin Total Daily Dose (TDD) Quartile			
		Quartile 1 ***n*** **= 10,312**	**Quartile 2** ***n*** **= 10,358**	**Quartile 3** ***n*** **= 10,283**	**Quartile 4** ***n*** **= 10,262**
Race, *n* (%)					
White/Caucasian [a]	25,460 (61.8)	5949 (57.7)	6194 (59.8)	6407 (62.3)	6910 (67.3)
African American	5830 (14.2)	1710 (16.6)	1626 (15.7)	1419 (13.8)	1075 (10.5)
Asian	893 (2.2)	322 (3.1)	214 (2.1)	194 (1.9)	163 (1.6)
Hispanic	87 (0.2)	17 (0.2)	33 (0.3)	22 (0.2)	15 (0.1)
Other/Unknown	8945 (21.7)	2314 (22.4)	2291 (22.1)	2241 (21.8)	2099 (20.5)
BMI, mean (SD), kg/m^2	34.1 (6.7)	31.0 (6.6)	33.4 (6.4)	35.1 (6.3)	37.0 (6.0)
Height, mean (SD), m	1.7 (0.1)	1.7 (0.1)	1.7 (0.1)	1.7 (0.1)	1.7 (0.1)
Weight, mean (SD), kg	98.3 (25.3)	87.5 (22.9)	95.6 (23.6)	101.1 (24.0)	109.7 (25.4)
US Census Region, *n* (%)					
Northeast	5261 (12.8)	1514 (14.7)	1393 (13.5)	1257 (12.2)	1097 (10.7)
Midwest	7494 (18.2)	1826 (17.7)	1834 (17.7)	1824 (17.7)	2010 (19.6)
South	19,844 (48.2)	4474 (43.4)	4917 (47.5)	5115 (49.7)	5338 (52.0)
West	8608 (20.9)	2497 (24.2)	2213 (21.4)	2085 (20.3)	1813 (17.7)
Unknown	8 (0.0)	1 (0.0)	1 (0.0)	2 (0.0)	4 (0.0)
CCI, mean (SD)	1.5 (1.8)	1.6 (1.9)	1.5 (1.8)	1.5 (1.7)	1.5 (1.7)
Comorbidities, *n* (%)					
Renal disease	8997 (21.8)	2619 (25.4)	2288 (22.1)	2103 (20.5)	1987 (19.4)
Pulmonary disease	7567 (18.4)	1682 (16.3)	1877 (18.1)	1926 (18.7)	2082 (20.3)
Congestive heart failure	5323 (12.9)	1445 (14.0)	1339 (12.9)	1237 (12.0)	1302 (12.7)
Peripheral vascular disease	4556 (11.1)	1249 (12.1)	1181 (11.4)	1069 (10.4)	1057 (10.3)
Cerebrovascular disease	3373 (8.2)	1019 (9.9)	870 (8.4)	798 (7.8)	686 (6.7)
Cancer	2850 (6.9)	836 (8.1)	724 (7.0)	663 (6.5)	627 (6.1)
Liver disease (mild)	2516 (6.1)	546 (5.3)	598 (5.8)	618 (6.0)	754 (7.4)
Myocardial infarction	1657 (4.0)	426 (4.1)	426 (4.1)	397 (3.9)	408 (4.0)
Rheumatic disease	1165 (2.8)	313 (3.0)	278 (2.7)	278 (2.7)	296 (2.9)
Dementia	696 (1.7)	296 (2.9)	184 (1.8)	130 (1.3)	86 (0.8)
Peptic ulcer disease	451 (1.1)	123 (1.2)	122 (1.2)	98 (1.0)	108 (1.1)
Liver disease (severe)	449 (1.1)	122 (1.2)	104 (1.0)	116 (1.1)	107 (1.0)
Hemiplegia or paraplegia	284 (0.7)	83 (0.8)	63 (0.6)	83 (0.8)	55 (0.5)
AIDS	156 (0.4)	50 (0.5)	47 (0.5)	34 (0.3)	25 (0.2)

[a] The raw data used the term "Caucasian"; however, it is likely that this group also included non-Caucasian White individuals. AIDS, acquired immunodeficiency syndrome; BMI, body mass index; CCI, Charlson comorbidity index; T2D, type 2 diabetes; TDD, total daily dose.

3.2. Total Daily Insulin Dose

After outliers representing the top and bottom 1% of TDD values were removed, mean TDD values during the post-index period ranged from 19 to 340 units (Figure 2). Overall, 23% of adults with T2D were prescribed a mean TDD of <50 units; 41% were prescribed 50–100 units; 21% were prescribed >100–150 units; and 15% were prescribed >150 units. The mean TDD for the study population was 96 units (SD, 58) and 1.0 units/kg (SD, 2.3); the median TDD was 80 units (interquartile range [IQR], 54–124 units). The overall mean of the minimum TDDs was 19 units, and the overall mean of the maximum TDDs was 99 units. Table 2 reports the average minimum and maximum values for each year and overall.

Table 2. Descriptive statistics for TDD among 41,215 people with T2D prescribed MDI during the study years and overall.

Year	N (%)	TDD (Units of Insulin)			
		Mean (SD)	**Median (IQR)**	**Min [a]**	**Max [a]**
2017	7121 (17.3)	95 (58)	80 (68)	19	98
2018	10,466 (25.4)	97 (58)	82 (71)	19	100
2019	11,551 (28.0)	100 (59)	85 (72)	19	102
2020	13,705 (33.3)	100 (59)	85 (74)	19	103
2021	12,933 (31.4)	100 (61)	84 (75)	19	102
2022 (6 months)	6635 (16.1)	98 (62)	81 (75)	19	101
Overall total	41,215 (100)	96 (58)	80 (71)	19	99

[a] The min and max TDD values represent the means of the minimum and of the maximum TDD values per patient/year (details in Methods section). Max, mean maximum TDD; MDI, multiple daily injections of insulin; Min, mean minimum TDD; SD, standard deviation; TDD, total daily dose of insulin.

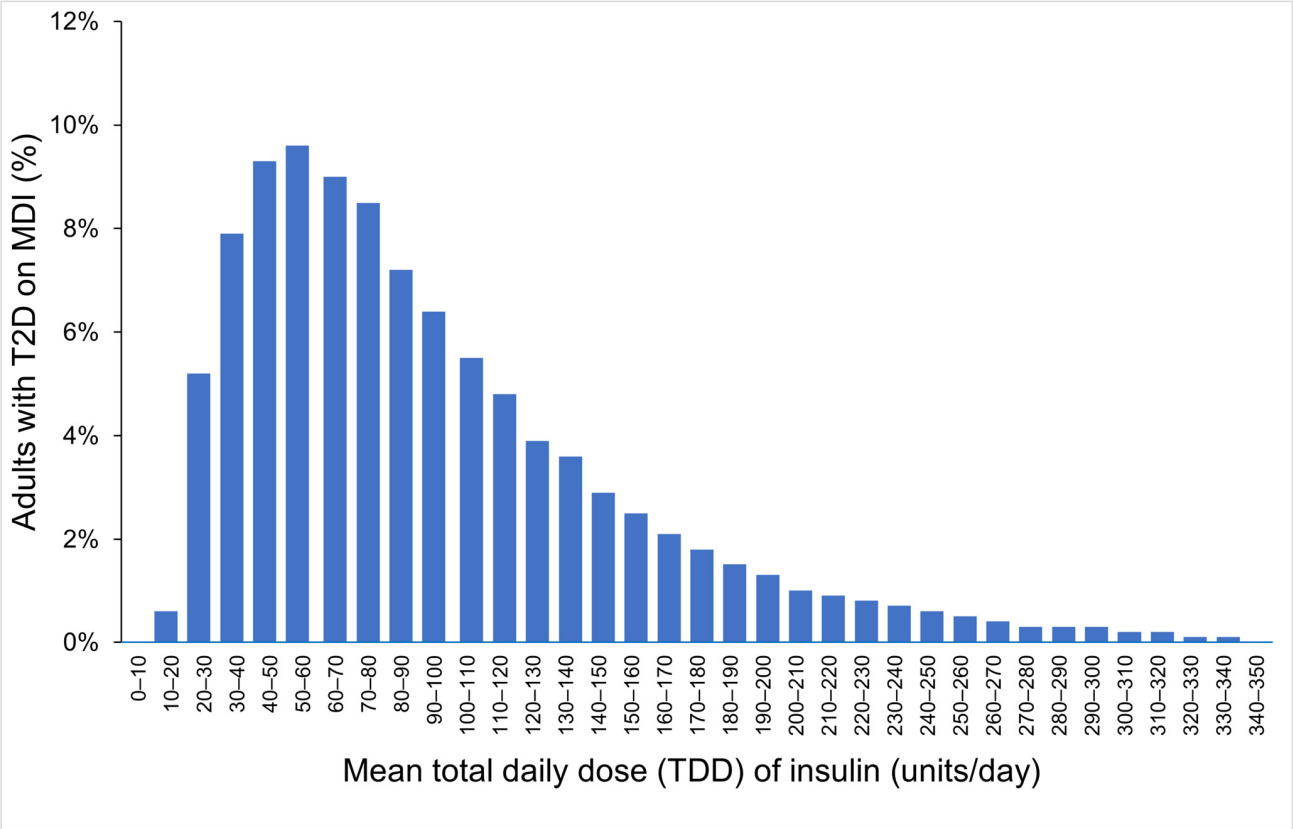

Figure 2. Distribution of individual mean TDD during post-index period (N = 41,215). MDI, multiple daily injections of insulin; T2D, type 2 diabetes; TDD, total daily dose of insulin.

3.3. Regression Analysis

Characteristics of the 41,215 individuals with T2D prescribed MDI are summarized in Supplemental Table S2 according to the categories used in the GLM regression analysis. The coefficient of multiple determination for the model (R^2) was 0.14, indicating that the model accounted for 14% of variation in TDD. The variance inflation factor was used to assess multicollinearity between the independent variables of the model. All variables had a variance inflation factor of <5, so multicollinearity was not considered to be an issue within our regression analyses.

There were several significant predictors of lower TDD. The regression results indicated that, on average, TDD was 7% lower among women than men; 15% lower among African American than White/Caucasian individuals, and from 8% to 19% lower in US Census Regions other than the South (Table 3; Supplemental Table S3). Moreover, TDD was found to be lower for those receiving certain noninsulin diabetes medications during the 6 months before the index date, namely, 6% lower for those with one or more sulfonylurea prescriptions (vs. none), 5% lower for those with one or more metformin prescriptions (vs. none), and 8% and 20% lower among those prescribed 2 or 3 noninsulin medications, respectively, versus no pre-index noninsulin medications (Table 3).

Significant predictors of greater TDD included BMI and being age 30–49 years or 50–64 years, associated with 7% and 12% greater TDD, respectively, as compared with ages ≥ 65 years (Table 3). Pre-index prescription(s) for an SGLT2 inhibitor or a GLP-1 RA were associated with 8% and 12% greater TDD compared with no such prescriptions.

Table 3. Generalized linear model regression results for association of variables with TDD.

Parameter	Reference [a]	TDD Ratio [b]	t-Value [c]	*p*-Value [d]
Intercept		30.26	183.39	<0.001
Sex: Female	Male	0.93	−10.89	<0.001
Age category				
Age 18–29 years	≥65 years	0.98	−0.97	0.33
Age 30–49 years		1.07	6.70	<0.001
Age 50–64 years		1.12	14.77	<0.001
Race				
African American	Caucasian/White	0.85	−15.69	<0.001
Other		0.98	−1.86	0.063
US Census Region				
Northeast	South	0.87	−13.53	<0.001
West		0.92	−9.30	<0.001
Midwest		0.92	−8.42	<0.001
Unknown		0.81	−0.76	0.45
BMI (for every 1 kg/m^2 increase)	--	1.03	56.95	<0.001
Pre-index prescriptions (≥1)				
Sulfonylurea	No sulfonylurea	0.94	−2.74	0.006
GLP-1 RA	No GLP-1 RA	1.12	5.99	<0.001
Metformin	No metformin	0.95	−3.04	0.002
SGLT2 inhibitor	No SGLT2 inhibitor	1.08	3.67	<0.001
No. of pre-index noninsulin meds [e]				
1	None (0)	0.98	−1.48	0.14
2		0.92	−2.19	0.028
≥3		0.80	−2.11	0.035

[a] Reference variables with an estimate of 0 and TDD ratio of 1.0 are the default values used in the analysis. Other categorical values are compared with the reference variables to estimate the size of the relative association with the dependent variable, TDD. [b] The TDD ratio value can be interpreted as the percentage difference from the reference variable (with value of 1.0), e.g., women have 7% lower TDD, on average, than men. [c] Higher absolute t-values indicate stronger evidence of a relationship between dependent and independent variables. [d] The *p*-value associated with the t-value. [e] The number of noninsulin glucose-lowering medications used (in addition to insulin), with the reference value of no (0) additional medications referring to patients who were prescribed only insulin. BMI, body mass index; GLP-1 RA, glucagon-like peptide-1 receptor agonist; meds, noninsulin diabetes medications; no., number; SE, standard error; SGLT2, sodium-glucose cotransporter 2; TDD, total daily dose of insulin.

4. Discussion

In this retrospective, observational US study, we found that 13.5% of ~3.3 million adults with T2D in the database had one or more basal insulin prescriptions, 6.2% had valid prescriptions for both basal and prandial insulin, and 1.2% were prescribed MDI, defined as ≥3 daily basal-plus-prandial insulin injections. The median TDD was 80 units of insulin, with range of 19 to 340 units (IQR, 54–124), among the 41,215 people prescribed MDI whom we studied; and the mean prescribed TDD was 96 units. Overall, 36% of people in the study were prescribed a TDD of >100 units.

Current ADA clinical practice recommendations for pharmacologic therapy note that many people with T2D require insulin daily doses of ~1 unit/kg [1], which was the mean prescribed TDD by weight in the present study (1.0 unit/kg). Prior publications reporting TDD for people with T2D include the randomized OpT2mise clinical trial, in which the mean baseline TDD was 1.1 units/kg/day (SD, 0.4) in both treatment groups of enrolled patients with T2D and poor glycemic control on MDI (≥3 injections/day; A1C level ≥ 8% and ≤12%) [21,22]. The total baseline mean TDD in OpT2mise was 112 and 106 units in pump therapy and MDI groups, respectively. In the prior 4-T (Treating to Target in Type 2 Diabetes) open-label clinical trial, patients who were taking two types of

insulin (3–4 injections per day) received a median TDD over 3 years of 79 to 105.5 units (0.86–1.21 units/kg) [23].

Our findings for a real-world population with T2D are not directly analogous to those for selected populations treated in the controlled conditions of clinical trials, such as OpT2mise and 4-T. However, we were unable, at the time of this writing, to identify other large-scale, real-world studies describing insulin doses as prescribed for people in the US with T2D using MDI. Similarly, with regard to the frequency of basal insulin and MDI prescribing for T2D, the findings of two earlier studies in US real-world settings are not directly comparable to those of the present study because of differences in eligibility criteria and endpoint definitions. Bonafede at al. found that 99,578 of 1,102,629 adults with T2D (9.0%) had initiated basal insulin in the study period from 2006 to 2012 (vs. 13.5% in the present study) [10]. Brixner et al. reported that, of 3.4 million people with T2D in 2012 to 2015, 168,884 (4.9%) were prescribed basal insulin, and 93,538 (2.7%) were prescribed MDI, defined as two pharmacy claims each for basal and bolus (prandial) insulin over a 12-month period [9]. Both of these studies drew on administrative claims data for commercially insured individuals [9,10], rather than on an aEMR database, as in the present study, which captured data for a broad population that included both commercially insured and Medicare patients.

Results of the GLM regression analysis identified several factors predicting a lower TDD in the present study, including female sex, African American race, and pre-index prescriptions of sulfonylurea, metformin, or 2 to 3 noninsulin glucose-lowering medications (versus none). Predictors of greater TDD included increasing BMI, age 30–64 years, and prescriptions for an SGLT2 inhibitor or GLP-1 RA during the 6-month pre-index period. While prescriptions for SGLT2 inhibitors and GLP-1 RAs may be discontinued [24,25], the findings regarding these noninsulin glucose-lowering agents were unexpected nonetheless. Moreover, we note that the analysis did not control for some potentially relevant factors, including time since the T2D diagnosis (disease duration), which could affect insulin requirements for achieving glycemic control. Other potentially relevant factors that are not readily available from an aEMR-derived database, such as socioeconomic status, access to healthcare resources, and patient education levels, could also have contributed to the variability in TDD. We elected not to include HbA1c in the model used for our study because of a concern about reverse causation, which could occur if HbA1c is treated as a predictor of TDD.

Strengths of this study include the use of a large, well-regarded, and well-maintained database that includes a geographically diverse US population. We utilized recent data, ending in mid-2022 over a study period of 5.5 years, assessing TDD for people with T2D prescribed MDI, contributing to a current understanding of insulin therapy as prescribed for T2D in US clinical practice.

As for all retrospective studies, however, the data may contain inaccuracies or missing information resulting from data entry errors, variations in coding practices, or incomplete documentation. Moreover, because no measure of continuous enrollment is available in the IQVIA dataset, clinical characteristics gathered in the pre-index period may not completely reflect all characteristics or prescribed medications. Thus, for the regression analyses, our model likely does not fully explain the variability in TDD, a supposition supported by the R^2 of only 0.14. For example, while the dataset captures prescription records within the time frame examined, prescriptions outside of that time frame are not captured; therefore, the complete list of medications prescribed for each patient over time is not available. This is particularly relevant with regard to prior prescriptions for noninsulin glucose-lowering agents, which would be expected for most people with T2D before instituting treatment intensification with insulin and eventually MDI [1,26]. Indeed, during the 6-month pre-

index look-back period, the majority of people on MDI in this study (87%) had no recorded prescriptions for noninsulin glucose-lowering agents (see Supplemental Table S2), a finding suggesting that the list of prior medications was likely incomplete.

Another study limitation is the fact that prescription records with missing or invalid information on dose or frequency of administration (e.g., stating "as directed by physician") were not considered because we required a clear prescription for insulin dose and frequency in order to identify people prescribed MDI and calculate the TDD. This requirement may have affected TDD estimates or resulted in underestimating the proportion prescribed MDI. Moreover, TDD is estimated based on the insulin dose and frequency information found in the Signa_txt data field. Calculated TDD may be overestimated from the true dose if a prescription is dosed up, a practice that may occur to ensure a patient has adequate insulin. Imputing basal or prandial insulin doses when missing may also have resulted in over- or underestimating TDD in light of potential changes in insulin dose or lack of adherence to insulin therapy [6–8]. In addition, the lower proportions of people prescribed MDI in 2017 and 2022 compared with other calendar years was likely because insulin prescriptions before 2017 and after 2022 were not considered for identifying the use of MDI. The exclusion of individuals prescribed U-500 and premixed insulin may also have resulted in underestimating the number of people prescribed MDI, as well as in affecting TDD estimates. Finally, adherence with therapy could not be assessed because, as for all prescription-based studies, we cannot be sure whether prescriptions were filled or taken as prescribed.

Basal insulin dose is likely dependent on blood glucose levels; therefore, further research evaluating the association between glycemic control and TDD is needed. Moreover, given that many factors can potentially affect TDD, additional research is warranted to explore other potentially relevant predictors. Studies of other large populations using different real-world data sources are needed to expand our understanding of TDD for people with T2D, ideally with a means to determine whether insulin is utilized as prescribed.

5. Conclusions

In this retrospective observational study of US adults with T2D, 1.2% were prescribed MDI in the period from 2017 to mid-2022. The individual mean TDD ranged from 19 to 340 units of insulin, with an overall median TDD of 80 units and mean TDD of 96 units. Significant predictors of TDD included both demographic and clinical characteristics, as well as other prescribed noninsulin medications. Future work will examine glycemic outcomes for these individuals with T2D prescribed MDI.

Supplementary Materials: The following supporting information can be downloaded at https://www.mdpi.com/article/10.3390/diabetology6020013/s1, Table S1: Number and percentage of adults with T2D in dataset by insulin type and MDI status, overall and by year (1 January 2017—1 July 2022); Table S2: Demographics and clinical characteristics of the 41,215 individuals with T2D prescribed MDI who were included in the generalized linear model regression analysis of variables associated with TDD; Table S3: Generalized linear model regression results for association of variables with TDD.

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Institutional Review Board Statement: This noninterventional study was conducted in accordance with the Declaration of Helsinki and was considered to be exempt from institutional review board approval because it was a retrospective analysis of deidentified data.

Informed Consent Statement: Patient consent was waived due to the use of deidentified data.

Data Availability Statement: The deidentified data that support the findings of this study were used under a licensing agreement from IQVIA (Durham, NC, USA) for the current study and are not publicly available. Interested researchers may contact IQVIA to apply for access to the study's data.

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References

1. American Diabetes Association Professional Practice Committee. 9. Pharmacologic approaches to glycemic treatment: Standards of Care in Diabetes-2024. *Diabetes Care* **2024**, *47*, S158–S178. [CrossRef] [PubMed]
2. Venkatraman, S.; Echouffo-Tcheugui, J.B.; Selvin, E.; Fang, M. Trends and disparities in glycemic control and severe hyperglycemia among US adults with diabetes using insulin, 1988–2020. *JAMA Netw. Open* **2022**, *5*, e2247656. [CrossRef] [PubMed]
3. Centers for Disease Control and Prevention. National Diabetes Statistics Report Website. Available online: https://www.cdc.gov/diabetes/php/data-research/index.html (accessed on 27 November 2024).
4. McGill, J.B.; Hirsch, I.B.; Parkin, C.G.; Aleppo, G.; Levy, C.J.; Gavin, J.R., 3rd. The current and future role of insulin therapy in the management of type 2 diabetes: A narrative review. *Diabetes Ther.* **2024**, *15*, 1085–1098. [CrossRef]
5. McCall, A.L. Insulin therapy and hypoglycemia. *Endocrinol. Metab. Clin. N. Am.* **2012**, *41*, 57–87. [CrossRef] [PubMed]
6. Skriver, L.K.L.; Nielsen, M.W.; Walther, S.; Norlev, J.D.; Hangaard, S. Factors associated with adherence or nonadherence to insulin therapy among adults with type 2 diabetes mellitus: A scoping review. *J. Diabetes Complicat.* **2023**, *37*, 108596. [CrossRef] [PubMed]
7. Peyrot, M.; Barnett, A.H.; Meneghini, L.F.; Schumm-Draeger, P.M. Insulin adherence behaviours and barriers in the multinational Global Attitudes of Patients and Physicians in Insulin Therapy study. *Diabet. Med.* **2012**, *29*, 682–689. [CrossRef]
8. Edelman, S.V.; Ermakova, A.; Xiong, Y.; Sieradzan, R.; Taylor, S.D. Persistence with basal-bolus insulin therapy in patients with type 2 diabetes mellitus and effect on clinical and economic outcomes: A retrospective claims database study. *J. Manag. Care Spec. Pharm.* **2019**, *25*, 1420–1431. [CrossRef] [PubMed]
9. Brixner, D.; Ermakova, A.; Xiong, Y.; Sieradzan, R.; Sacks, N.; Cyr, P.; Taylor, S.D. Clinical and economic outcomes of patients with type 2 diabetes on multiple daily injections of basal-bolus insulin (MDI) therapy: A retrospective cohort study. *Clin. Ther.* **2019**, *41*, 303–313.e1. [CrossRef]

10. Bonafede, M.; Chandran, A.; DiMario, S.; Saltiel-Berzin, R.; Saliu, D. Medication usage, treatment intensification, and medical cost in patients with type 2 diabetes: A retrospective database study. *BMJ Open Diabetes Res. Care* **2016**, *4*, e000189. [CrossRef] [PubMed]
11. American Diabetes Association Professional Practice Committee. 6. Glycemic goals and hypoglycemia: Standards of Care in Diabetes-2024. *Diabetes Care* **2024**, *47*, S111–S125. [CrossRef] [PubMed]
12. Sun, H.; Saeedi, P.; Karuranga, S.; Pinkepank, M.; Ogurtsova, K.; Duncan, B.B.; Stein, C.; Basit, A.; Chan, J.C.N.; Mbanya, J.C.; et al. IDF Diabetes Atlas: Global, regional and country-level diabetes prevalence estimates for 2021 and projections for 2045. *Diabetes Res. Clin. Pract.* **2022**, *183*, 109119. [CrossRef] [PubMed]
13. Wagenknecht, L.E.; Lawrence, J.M.; Isom, S.; Jensen, E.T.; Dabelea, D.; Liese, A.D.; Dolan, L.M.; Shah, A.S.; Bellatorre, A.; Sauder, K.; et al. Trends in incidence of youth-onset type 1 and type 2 diabetes in the USA, 2002-18: Results from the population-based SEARCH for Diabetes in Youth study. *Lancet Diabetes Endocrinol.* **2023**, *11*, 242–250. [CrossRef]
14. Basu, S.; Yudkin, J.S.; Kehlenbrink, S.; Davies, J.I.; Wild, S.H.; Lipska, K.J.; Sussman, J.B.; Beran, D. Estimation of global insulin use for type 2 diabetes, 2018–30: A microsimulation analysis. *Lancet Diabetes Endocrinol.* **2019**, *7*, 25–33. [CrossRef] [PubMed]
15. American Diabetes Association Professional Practice Committee. 7. Diabetes technology: Standards of Care in Diabetes-2024. *Diabetes Care* **2024**, *47*, S126–S144. [CrossRef] [PubMed]
16. IQVIA Ambulatory EMR-US. Available online: https://www.iqvia.com/locations/united-states/library/fact-sheets/iqvia-ambulatory-emr-us (accessed on 27 November 2024).
17. US Department of Health & Human Services. Summary of the HIPAA Privacy Rule (Health Insurance Portability and Accountability Act of 1996). Available online: https://www.hhs.gov/hipaa/for-professionals/privacy/laws-regulations/index.html (accessed on 27 November 2024).
18. US Food & Drug Administration (FDA). National Drug Code Directory. Available online: https://www.fda.gov/drugs/drug-approvals-and-databases/national-drug-code-directory (accessed on 27 November 2024).
19. Quan, H.; Sundararajan, V.; Halfon, P.; Fong, A.; Burnand, B.; Luthi, J.C.; Saunders, L.D.; Beck, C.A.; Feasby, T.E.; Ghali, W.A. Coding algorithms for defining comorbidities in ICD-9-CM and ICD-10 administrative data. *Med. Care* **2005**, *43*, 1130–1139. [CrossRef] [PubMed]
20. Census Regions and Divisions of the United States. Available online: https://www2.census.gov/geo/pdfs/maps-data/maps/reference/us_regdiv.pdf (accessed on 27 November 2024).
21. Conget, I.; Castaneda, J.; Petrovski, G.; Guerci, B.; Racault, A.S.; Reznik, Y.; Cohen, O.; Runzis, S.; de Portu, S.; Aronson, R. The impact of insulin pump therapy on glycemic profiles in patients with type 2 diabetes: Data from the OpT2mise study. *Diabetes Technol. Ther.* **2016**, *18*, 22–28. [CrossRef]
22. Aronson, R.; Reznik, Y.; Conget, I.; Castaneda, J.A.; Runzis, S.; Lee, S.W.; Cohen, O. Sustained efficacy of insulin pump therapy compared with multiple daily injections in type 2 diabetes: 12-month data from the OpT2mise randomized trial. *Diabetes Obes. Metab.* **2016**, *18*, 500–507. [CrossRef] [PubMed]
23. Holman, R.R.; Farmer, A.J.; Davies, M.J.; Levy, J.C.; Darbyshire, J.L.; Keenan, J.F.; Paul, S.K. Three-year efficacy of complex insulin regimens in type 2 diabetes. *N. Engl. J. Med.* **2009**, *361*, 1736–1747. [CrossRef]
24. Alkabbani, W.; Shah, B.R.; Zongo, A.; Eurich, D.T.; Alsabbagh, M.W.; Gamble, J.M. Post-initiation predictors of discontinuation of the sodium-glucose cotransporter-2 inhibitors: A comparative cohort study from the United Kingdom. *Diabetes Obes. Metab.* **2023**, *25*, 3490–3500. [CrossRef]
25. Malik, M.E.; Falkentoft, A.C.; Jensen, J.; Zahir, D.; Parveen, S.; Alhakak, A.; Andersson, C.; Petrie, M.C.; Sattar, N.; McMurray, J.J.V.; et al. Discontinuation and reinitiation of SGLT-2 inhibitors and GLP-1R agonists in patients with type 2 diabetes: A nationwide study from 2013 to 2021. *Lancet Reg. Health Eur.* **2023**, *29*, 100617. [CrossRef]
26. Davies, M.J.; Aroda, V.R.; Collins, B.S.; Gabbay, R.A.; Green, J.; Maruthur, N.M.; Rosas, S.E.; Del Prato, S.; Mathieu, C.; Mingrone, G.; et al. Management of hyperglycemia in type 2 diabetes, 2022. A Consensus Report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). *Diabetes Care* **2022**, *45*, 2753–2786. [CrossRef]