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Calculated Daily Insulin Dosages Overestimate Prescribed Insulin Doses in Type 2 Diabetes: A Primary Care Database Study

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Abstract

Background: The aim was to compare the prescribed and calculated daily insulin dosages based on prescription data in type 2 diabetes patients in a general practice database.

Methods: A total of 17782 type 2 diabetes patients (age: 70.0 ± 11.5 years; 52% males; 16% diabetologist care) with ≥2 insulin prescriptions from 834 practices were analyzed (Disease Analyser: 01/2011-12/2015). Prescribed daily dosage (PDD) (physician documentation) and calculated daily dose (CDD) (pack size × strength × volume / days between 2 prescriptions) were calculated for short-acting, long-acting, and premixed insulins. PDD and CDD were compared using paired *t*-tests. Linear regression models assessed the associations of insulin dosage difference (CDD-PDD) with age, sex, diabetologist care, private health insurance, obesity, HbA1c, hypertension, hyperlipidemia, macro- and microvascular complications.

Results: Mean [SD] CDDs were higher than PDDs for short-acting (52 [28] vs 48 [26] units/day), long-acting (30 [20] vs 24 [15] units/day), and premixed (46 [26] vs 40 [21] units/day) insulins (all $P < .05$). In regression models, age (per year) was associated with higher CDD-PDD differences (+0.11, +0.04, +0.10; $P < .01$) for short-, long-acting, and premixed insulins, respectively. Diabetologist care was related to lower differences (–2.92, –1.02, –3.65; all $P < .05$). HbA1c was associated with higher differences in long-acting and premixed insulins, but was related to a lower difference in short-acting insulins (all $P < .05$).

Conclusions: CDD in primary care database studies substantially overestimate the PDD (8-25%). Age, diabetologist care, and glycemic control were related to CDD-PDD differences. Priming and safety shots with pens, dosing errors, or the accumulation of insulin reserves by patients may be underlying reasons.

Keywords

adherence, diabetes, insulin, primary care, daily dose

Insulin prescriptions are often necessary to reach the individual HbA1c targets in patients with type 2 diabetes.[1] A single injection of low dosage basal insulin in addition to oral glucose-lowering drugs is mostly used at the beginning, but over time many patients require intensification of insulin therapy (short-acting insulins, premixed insulins) with increasing daily insulin dosages.[1] Observational studies have reported a relationship between insulin use and cardiovascular events in diabetes patients.[2-4] This association has been mostly attributed to reverse causality, because the insulin-treated patients were already at an increased risk of cardiovascular events at onset of insulin therapy compared to patients on oral glucose-lowering drugs.[2] However, a case-control study using a large pharmacoepidemiological database including only insulin-treated patients found an increased cardiovascular risk with higher daily insulin dosages.[3] In contrast, in randomized clinical trials (eg, ACCORD), no relationship between daily insulin dosage and cardiovascular death was observed after adjustment for severe hypoglycemia, weight change, attained HbA1c, and other baseline risk factors.[5] One important difference between the observational studies and the RCT is that daily insulin dosage was calculated based on prescription data in the first and is documented by physician records in the latter.

To the best of our knowledge, there are no studies that have compared calculated daily insulin dosages in health

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care databases with the prescribed daily insulin dose documented by physicians. The primary aim of our study was to compare the calculated (CDD) and prescribed (PDD) daily insulin dosages in insulin-treated type 2 diabetes patients in primary care and diabetologist practices. In addition, we have explored the relationship between demographic and clinical factors, in particular, macro- and microvascular complications, with the difference between CDD and PDD.

Methods

Study Population

The German Disease Analyzer database (IMS Health, Frankfurt) includes patient data entered by general practitioners and internal medicine practices throughout Germany.[6,7] Practices are anonymously reporting all diagnoses (ICD-10), prescriptions (Anatomical Therapeutic Chemical Classification System), hospital admissions, and laboratory test results on an ongoing basis. The validity and representativeness of the Disease Analyzer database have been shown previously.[6]

The current study sample included type 2 patients (ICD-10: E11) from 834 practices who received at least 2 insulin prescriptions during the index period used for this study (January 2011 to December 2015).

Demographic data included age, sex, health insurance (private/statutory), and type of diabetes care (diabetologist/general practitioner). Data on HbA1c and body mass index, which were documented by the practices, were also analyzed. Macrovascular complications were determined based on primary care diagnoses (ICD-10 codes) for coronary heart disease (I20, I24, I25), myocardial infarction (I21, I22, I23, I25.2), stroke (I63, I64, G45), and peripheral vascular disease (E11.5, E14.5, I73.9). Microvascular complications included retinopathy (E11.3, E14.2), neuropathy (E11.4, E14.4), and nephropathy (E11.2, E14.2, N18, N19). Lipid disorders and hypertension were also assessed.

Study Outcomes

Only patients with known daily prescribed insulin documented by the physicians were included. The calculated daily insulin dose (CDD) was assessed using prescription information (pack size × strength × volume divided by number of days between 2 subsequent prescriptions) of the same insulin group (short-acting, long-acting, premixed). For CDD mean values were calculated per patient over the whole therapy time (minimum 2 months, maximum 5 years). For PDD also mean values were estimated over the whole therapy time.

Statistical Analyses

Descriptive statistics were given and differences in CDD and PDD were assessed using paired *t*-tests. Linear regression models with the calculated difference between CDD and PDD as dependent variable were fitted, separately for short-acting, long-acting and premixed insulins. Sex, age, type of health insurance, type of diabetes care, HbA1c, obesity, hypertension, hyperlipidemia, and macro- and microvascular complications were entered as independent variables. *P* values < .05 were considered as statistically significant. The analyses were carried out using SAS version 9.3.

Table 1. Baseline Characteristics of Type 2 Diabetes Patients With Insulin Prescriptions and Documented Dose Information (Disease Analyser).

Variable	Value
N	17782
Age (years)	70.0 (11.5)
Male sex (%)	51.5
Short-acting insulins (%)	23.1
Long-acting insulins (%)	58.4
Premixed insulins (%)	18.5
Private health insurance (%)	4.6
Diabetologist care (%)	15.6
HbA1c %	8.2 (1.6)
Obesity (BMI ≥30 kg/m^2) (%)	59.1
Peripheral neuropathy (%)	31.7
Retinopathy (%)	10.0
Nephropathy (%)	25.5
Hypertension (%)	80.5
Hyperlipidemia (%)	54.1
Myocardial infarction (%)	5.3
Stroke including TIA (%)	10.6
Coronary heart disease (%)	34.1
Peripheral vascular disease (%)	21.3

Data are means (SD) or proportions (%).

Results

After applying the inclusion criteria, 17782 insulin-treated type 2 diabetes patients were selected. The baseline clinical characteristics are given in Table 1. The mean age was 70 years, and slightly more men than women were included. About 60% were treated with long-acting insulins and about a quarter received short-acting insulins (mostly in combination with long-acting insulins). Basal insulin intensification can also be done by adding of GLP-1-agonists/DPP-4 inhibitors/SGLT2 inhibitors/thiazolidinediones before adding bolus insulin. Only 19% were treated with premixed insulin preparations. There was a low prevalence of privately insured patients. Although about 16%of the patients were mainly in diabetologist care, the average HbA1c indicated an inadequate glycemic control. Overall, 89% of study patients received prescriptions for self-monitoring of blood glucose during the study period.

Of the patients, 60% were obese. In all, 80% had diagnosed hypertension, and about half of the group had lipid disorders. Microvascular complications were already present

Table 2. Prescribed Daily Dose (PDD) and Calculated Daily Dose (CDD) in Insulin-Treated Type 2 Diabetes Patients in Primary Care.

	Short-acting insulins (n = 5119)		*Long-acting insulins (n = 12977)*		*Premixed insulins (n = 4117)*	
Group	PDD	CDD	PDD	CDD	PDD	CDD
All patients (N = 18154)	47.9 (25.9)*	51.9 (28.4)*	23.7 (14.5)*	29.9 (20.0)*	39.9 (21.2)*	45.5 (25.8)*
General practices (N = 15329)	48.0 (26.3)*	52.6 (28.6)*	23.8 (14.6)*	30.2 (20.3)*	40.2 (21.3)*	46.2 (25.9)*
Diabetologists (N = 2825)	47.5 (24.2)*	48.5 (27.3)*	23.4 (13.9)*	28.7 (18.8)*	36.7 (19.5)*	39.0 (23.5)*
Male patients (N = 9345)	48.5 (25.7)*	52.9 (29.0)*	23.7 (14.5)*	29.8 (20.0)*	40.4 (21.3)*	45.6 (26.1)*
Female patients (N = 8809)	47.4 (26.2)*	50.8 (27.7)*	23.7 (14.5)*	30.1 (20.0)*	39.4 (21.1)*	45.3 (25.5)*
Age ≤60 years (N = 4006)	50.1 (27.0)*	51.5 (30.2)*	24.9 (15.2)*	30.7 (20.3)*	44.3 (23.2)*	47.3 (26.8)*
Age 61-70 years (N = 4431)	49.5 (26.0)*	53.9 (28.7)*	25.4 (15.3)*	31.4 (20.7)*	42.6 (22.6)*	47.5 (27.1)*
Age 71-80 years (N = 6296)	48.0 (25.6)*	52.3 (27.4)*	23.1 (13.9)*	29.4 (19.5)*	41.1 (21.5)*	47.0 (25.5)*
Age >80 years (N = 3421)	41.3 (23.7)*	47.8 (26.7)*	19.8 (12.2)*	26.9 (19.0)*	35.8 (18.7)*	42.1 (24.7)*

Data are mean (SD).
*$P < .05$ PDD vs CDD (paired *t*-tests).

in a substantial number. About one-third had diagnosed peripheral neuropathy and in a quarter nephropathy was found. Coronary heart disease was already observed in about one-third of the population. Myocardial infarction and stroke was diagnosed in 5% and 10%, respectively. Finally, about 20% had diagnosed to peripheral vascular arterial disease.

The mean PDD and CDD for short-acting, long-acting, and premixed insulins are given in Table 2. For all 3 insulin groups the CDDs were significantly higher than the PDDs (short-acting: +8%, long-acting: +26%, premixed insulins: +14%). Average CDDs were consistently higher than PDDs after stratifying the patients by type of care (general practice, diabetologist), sex, and age (4 groups) (Table 2).

In Table 3 the results of the multivariable linear regression models (dependent variable: difference CDD-PDD) are shown. After adjustment, for each year of age, the CDD-PDD-difference was higher by 0.11, 0.04, and 0.10 for short-acting, long-acting, and premixed insulins, respectively. Furthermore, per 1% HbA1c, the difference was higher by 0.47 in long-acting insulins and by 0.56 in premixed insulin users. In contrast, HbA1c was related to a lower difference (–0.77) in short-acting users. Diabetologist care (reference: general practice) was associated with lower difference for all 3 insulin groups (Table 3). The mean (± SD) HbA1c of patients in diabetologist care (8.3 ± 1.6%) was not different from patients treated in general practices (8.2 ± 1.6%) ($P \geq .05$).

Presence of macro- or microvascular complications was not significantly related to CDD-PDD-differences, as well as hypertension (except in long-acting insulin users) and hyperlipidemia. Finally, there were no significant associations between sex, private health insurance, obesity, and the difference in CDD and PDD.

Discussion

This study represents the first evaluation of the relationship between the calculated daily insulin dosage based on available data from a general practice database with the actual prescribed dosage based on physician records. The results indicate that CDD, which is often used in pharmacoepidemiological studies, generally overestimates the PDD given by the physicians. Our results also provide information on clinical characteristics related to the CDD-PDD-difference. Age and HbA1c (except for short-acting insulins) were associated with higher differences, whereas diabetologist care was related to a lower difference. Macro- or microvascular complications, which are often outcomes in pharmacoepidemiological studies in diabetes, were not associated with CDD-PDD difference. Finally, both CDD and PDD were higher in patients treated in general practices than in diabetologist care.

The underlying reasons for the discrepancy between CDD and PDD need to be further explored. Most likely, several factors explain why calculations of daily insulin dosages based on prescription data often overestimate the actual prescribed dose. Previous studies have shown that most but not all insulin-treated diabetes patients (77%) make efforts to regularly take insulin on a daily basis.[8] Furthermore, it has been estimated that 12-19% of prescribed insulin is lost due to wastage in syringe fillings and errors with drawing dosages.[9] However, this estimate may not apply to all patients, in particular, not to those using modern insulin pens. Most user of insulin pens carry out priming and safety shots with pens, which may take 6 to 8 IU for priming when a new pen is used and about 1 to 2 IU for safety shots before each injection, which is another potential explanation for the difference of CDD and PDD.

The refill adherence of repeat prescriptions of diabetes drugs have been shown to be higher than for other chronic diseases.[10] In the present study, older age was associated with a larger discrepancy between CDD and PDD in this study. It is conceivable, that insulin reserves could be more often accumulated in older patients, in particular, because insulin is often applied by nursing services and they require that insulin is always available for the patients.

Furthermore, diabetes patients in diabetologist care may be more familiar with insulin applications and with diabetes care in general than patients in general practices. Diabetologist

Table 3. Multivariable Linear Regression Models (Dependent Variable: Calculated/Prescribed Daily Insulin Dose) in Insulin-Treated Type 2 Diabetes Patients in Primary Care.

Variable	Short-acting insulins	Long-acting insulins	Premixed insulins
Age (per year)	0.11 (<0.01)	0.04 (<0.01)	0.10 (<0.01)
Male sex	1.40 (0.07)	–0.19 (0.55)	–0.31 (0.67)
Private health insurance (yes/no)	1.18 (0.58)	–0.41 (0.56)	0.23 (0.90)
Diabetologist care (yes/no)	–2.92 (<0.01)	–1.02 (0.02)	–3.65 (<0.01)
HbA1c (%)	–0.77 (0.01)	0.47 (<0.01)	0.56 (0.03)
Obesity (BMI ≥ 30 kg/m^2) (yes/no)	1.38 (0.39)	–0.62 (0.35)	1.96 (0.24)
Hypertension (yes/no)	1.20 (0.25)	0.01 (<0.01)	–0.79 (0.40)
Hyperlipidemia (yes/no)	–0.17 (0.82)	0.31 (0.31)	–0.60 (0.41)
Macrovascular complications (yes/no)	0.37 (0.64)	0.73 (0.72)	–0.91 (0.23)
Microvascular complications (yes/no)	–0.75 (0.34)	0.56 (0.56)	0.47 (0.52)

Data are ß-regression coefficients (*P* values). R^2: short-acting insulin model: .004, long-acting insulin model: .001; premixed insulin model: .004. Macrovascular complications: myocardial infarction, stroke, coronary heart disease, or peripheral vascular disease. Microvascular complications: peripheral neuropathy, retinopathy, or nephropathy.

care was related to a lower discrepancy between CDD and PDD. Higher HbA1c, indicating inadequate glycemic control and probably also a lower compliance with insulin therapy, was associated with a higher discrepancy between CDD and PDD, except for short-acting insulins (lower difference). Some of the patients with inadequate glycemic control may not fully comply with the prescribed insulin dosages given by the physicians, for example, they decide to take higher insulin doses to improve their hyperglycemia. On the other hand, the reason for the association between higher HbA1c and a higher difference between CDD and PDD maybe clinical inertia by prescribing physicians, for example, barriers currently preventing earlier initiation of insulin therapy in patients with type 2 diabetes.[11] Insulin therapy is often delayed for years.[12]

Finally, it is noteworthy, that macro- and microvascular complications were not related to differences in CDD and PDD. Therefore, a bias in investigating the association between insulin dosage and macro- or microvascular outcomes in database studies using CDD instead of PDD is not supported by this study.[3,4] It is noteworthy that both CDD and PDD were higher for all insulin groups in patients treated in general practices than in diabetologist care. The underlying reasons for this difference are unclear and need to be investigated in further studies.

Several limitations of the present study should be mentioned. First, no valid information on diabetes type and diabetes duration was available in the database. Also assessment of macro- and microvascular comorbidity relied on ICD codes by primary care physicians only. Finally, measurements of HbA1c and body mass index values were not standardized. Unfortunately, there was no information on the percentage of continuous subcutaneous insulin infusion users or the use of continuous glucose monitoring. Unfortunately, primary care databases like the Disease Analyser include no information on training and educational aspects, for example, with respect to insulin dose calculators. The strength of the study is the large nationwide database and the unbiased assessment of prescriptions.

In conclusion, the present study indicates that calculated daily insulin based on prescription information in database studies overestimate the actual prescribed dosages provided by physicians by 8% to 25%. Age and glycemic control were related to larger CDD-PDD-differences, whereas in diabetologist care lower differences were observed. Further studies need to determine the underlying reasons, including priming and safety shots with insulin pens, dosing errors, or the accumulation of insulin reserves by patients or nurses.

Abbreviation

CDD, calculated daily dosage; PDD, prescribed daily dosage.

Declaration of Conflicting Interests

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