Weight gain associated with insulin detemir vs insulin glargine in clinical practice: A retrospective longitudinal cohort study

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Purpose. In comparative randomized studies, use of insulin detemir has been consistently demonstrated to be associated with less weight gain than the industry standard, insulin glargine. However, the magnitude of the relative reduction in weight gain with use of insulin determir vs insulin glargine in regulatory studies (reported values ranged from 0.77 kg to 3.6 kg) may not be generalizable to patients in real-world practice conditions. A study was conducted to substantiate detemir's purported weight-sparing advantage over insulin glargine in newly treated patients with type 2 diabetes mellitus under the conditions found in a clinical practice setting.

Methods. A retrospective longitudinal cohort study design was applied in reviewing electronic medical records to identify insulin-naive, overweight patients with type 2 diabetes who received insulin detemir or insulin glargine therapy continued for up to 1 year. Patient weights at baseline and at each subsequent clinic visit after treatment initiation were identified. The primary outcome was the maximum weight increase from baseline after exposure to insulin detemir or glargine. The difference-in-differences (DiD) mean total body weight change was tested by analysis of covariance (ANCOVA).

Results. One hundred nine patient records (56 of patients who received insulin glargine and 53 of patients who received insulin detemir) met study criteria and underwent full abstraction. The covariate-adjusted estimated mean change in body weight associated with use of insulin detemir vs insulin glargine was –1.5 kg (95% CI, –2.89 to –0.12 kg; $P = 0.04$).

Conclusion. The mean weight gain associated with detemir use was significantly less than the mean weight change observed with glargine use. The magnitude of weight change was consistent with that demonstrated in randomized controlled trials. These results further substantiate detemir's purported comparative weight-sparing properties under conditions found in a real-world practice setting.

Keywords: diabetes mellitus type 2, drug side effect, insulin, insulin detemir, insulin glargine, weight gain

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Insulin-associated weight gain is a challenging problem, particularly in the treatment of overweight patients with type 2 diabetes mellitus. Among the available long-acting insulin preparations, insulin detemir (referred to as "detemir" hereafter) has been consistently demonstrated to reduce weight gain (ie, to have weight-sparing effects) in randomized studies comparing it against the industry standard, insulin glargine ("glargine" hereafter).[1-8] Detemir is considerably less utilized by prescribers, suggesting that prescribers are unaware or not fully convinced of the biological plausibility of this potential therapeutic advantage.[9,10] Additionally, the magnitude of detemir's weight-sparing effects may not be completely generalizable to patients in real-world practice conditions without the

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constraints of regulatory studies. The purpose of the study described here was to evaluate detemir's comparative weight-sparing effects in insulin-naive patients with type 2 diabetes under the conditions and constraints found in a real-world practice setting.

Insulin therapy, while providing effective glycemic control, often results in weight gain. Insulin-associated weight gain is particularly problematic in patients with type 2 diabetes because a majority (80%-90%) of these patients are already overweight or obese at the time of insulin initiation.[11] The weight gain associated with insulin therapy has deleterious effects that undermine some of the benefits of glycemic control; these effects include worsened insulin resistance, blood pressure elevation, unfavorable cholesterol changes, depression, and cardiovascular events, all of which contribute to increased morbidity and mortality. Perhaps the most detrimental effects of insulin-associated weight gain are the negative influences on motivation to start insulin therapy and patient adherence once insulin is initiated. The mere possibility of weight gain is recognized as a major psychological barrier to insulin initiation by both patients and prescribers (the term *psychological insulin resistance* refers to the reluctance of patients to use insulin that can result from fear of weight gain).[12,13] An insulin with a reduced propensity to promote weight gain would be highly desirable, and its use could potentially improve patient adherence and outcomes.

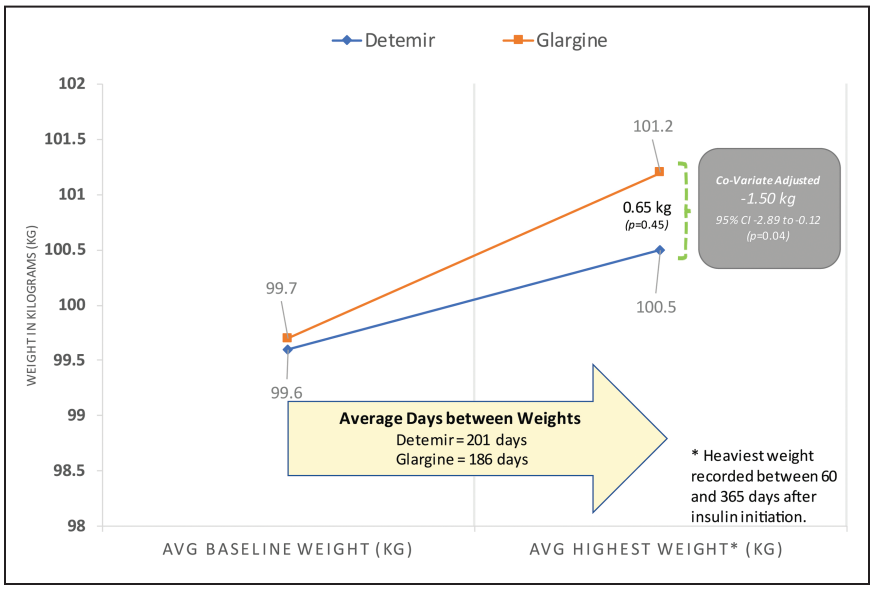
KEY POINTS

- A study was conducted to substantiate insulin detemir's purported weight-sparing advantage over insulin glargine in newly treated patients with type 2 diabetes under real-world practice conditions.
- The covariate-adjusted estimated mean change in body weight associated with detemir use vs glargine use was –1.5 kg (95% CI, –2.89 to –0.12 kg; $P = 0.04$) in favor of insulin detemir.
- The mean weight gain associated with insulin detemir use was significantly less than that with use of insulin glargine, and the magnitude of reduction of weight gain was consistent with values reported in randomized comparative trials.

Detemir is a long-acting insulin analogue that has been reported to have a reduced propensity to promote weight gain in type 2 diabetes compared to glargine. Detemir and glargine both provide relatively peak-free insulin concentrations over time relative to older insulin types, resulting in therapeutically similar blood glucose control and less frequent hypoglycemia. Detemir and glargine are similar in cost and availability. Seven randomized, head-to-head, open-label comparisons of detemir and glargine in patients with type 2 diabetes have been conducted.[1-7] Each study demonstrated significantly less weight gain among patients receiving detemir therapy, with a mean weight sparing of 0.77 to 3.6 kg after 6 months to 1 year of use. A recent meta-analysis affirmed detemir's favorable weight-sparing profile relative to all insulin comparators, including glargine.[8]

Many clinicians remain skeptical of the generalizability of detemir's weight-sparing advantage. Insulin therapy for patients in the variable conditions of clinical practice is often complicated by

Figure 1. Average differences-in-differences weight gain in the insulin detemir group vs insulin glargine group.



chronic illnesses, concomitant medication use, and poor access to other healthcare resources such as dieticians, all of which have a great influence on the magnitude of insulin-associated weight gain. Studies demonstrating detemir's comparatively greater weight-sparing effects were conducted under the intensity and scrutiny of controlled conditions, and the results may not be fully translatable to real-world practice. To our knowledge, the study described here was the first attempt to validate the weight-sparing properties of detemir reported in clinical trials involving patients who were treated in usual and customary clinical care settings.

Methods

Study design. In the study we applied a quasi-experimental design to a retrospective longitudinal cohort of patient records data on insulin use during the course of regular medical treatment of adults with type 2 diabetes. The cohort was identified by querying the available electronic medical record (EMR) for any patient with a prescription for detemir or glargine from January 2007 through 2014. Identified records were randomly selected for preliminary review using randomization software. Abstractors reviewed these records to determine study eligibility. Eligibility required that a patient have no previous or concurrent exposure to other insulin types, have a preexisting clinic record of contact with the healthcare system of sufficient duration to assess the primary outcome, and have a stable baseline weight. Contact with the healthcare system prior to insulin exposure was defined as 2 office visits at least 6 months prior to insulin initiation and at least 1 office visit 3 or more months after insulin initiation. Stable baseline weight was defined as having 2 weight measurements at least 60 days apart that did not differ by more than 3%, with those weights recorded no more than 6 months prior to insulin exposure, and at least 1 weight measurement recorded less than 30 days prior to insulin initiation.[14] Patient records indicating comorbidities or use of medications associated with variable or frequent weight change due to water retention or edema were excluded. Patient records meeting all preliminary inclusion criteria and no exclusion criteria underwent full abstraction. Records were randomly selected for preliminary review until sufficient records were identified to meet the a priori sample size for both the detemir and glargine groups. The study was reviewed and approved by the appropriate institutional review board.

Environment and database. The EMR from a rural community health center served as the existing data set for this study. This clinic provides affordable healthcare to approximately 13,000 patients annually, 60% of whom were uninsured during the study period. Of these patients, approximately 30% were users of basal insulin (detemir or glargine).The EMR combines practice management, chart review, order management, and documentation of all patient encounters and communications.

Outcomes. The primary outcome of interest was the greatest weight increase occurring within 1 year of continued exposure to basal insulin. Difference in differences (DiD) nomenclature was used to compare weight changes in the detemir and glargine groups. Change in body weight was determined by subtracting a patient's stable baseline weight from the highest recorded weight. The highest recorded weight was defined as the heaviest weight recorded within a time frame of at least 60 days but no more than 1 year after continued insulin exposure. Time (in days) between the weight measures was also collected to normalize results to days of insulin exposure. Continued insulin exposure was determined by the presence of detemir or glargine on the active medication list associated with each weight measurement recorded.

Secondary measures collected during abstraction included demographics (age, gender, race, and health insurance status), pre- and postexposure body mass index (BMI) and glycosylated hemoglobin (HbA_{1c}) levels, preexisting comorbidities, concurrent medications, and beginning and final insulin doses. BMI measurements were obtained at the same time as pre- and postexposure weight measurements. The preexposure HbA_{1c} level was defined as the value documented closest to the date of baseline weight documentation but not more than 180 days prior to insulin exposure. The postexposure HbA_{1c} level was defined as the value collected nearest to the date of the highest recorded weight but not less than 90 days after insulin exposure. Concurrent comorbidities were identified by common name, and International Classification of Diseases, Ninth Revision, Clinical Modification codes were collected from the patients' respective problem lists within 30 days of insulin initiation. Information on chronic medication use was obtained from a patient's medication list obtained from records of visits within 7 days of insulin exposure that persisted to the time of the highest weight measurement. Medications dropped from the list between the 2 weight measurements were not recorded. The absence of any or all secondary measures did not exclude a patient record from the study.

Abstraction protocol. The chart abstraction instrument (collection tool) was designed and implemented using a secure, web-based application. Two second-professional-year pharmacy students were trained as chart abstractors and were blinded to study aims and hypotheses to minimize bias during the preliminary screening and data abstraction.

A reviewer manual and standardized data abstraction instruments were provided to minimize inconsistent chart abstraction. The reviewer manual listed inclusion and exclusion criteria, primary and secondary measures, the required protocol for data abstraction, and management procedures for resolving any conflicts. The principal investigator conducted an audit to test interrater reliability after

every 25 records were abstracted. Ten records were randomly selected, and the highest weight (the most crucial measurement) was audited directly from the record. Audit results were compared to abstractor results using an intraclass correlation (ICC) test. An ICC of ≥97.5% was deemed acceptable. An ICC of <97.5% prompted a review of all 25 records and subsequent retraining of abstractors and correction of inconsistencies.

Sample size. Sample size per group was estimated assuming group standard deviations for DiD weight change of 6.07 for the detemir group and 6.34 for the glargine group.[3] Estimates were based on a 1-sided test to detect a mean DiD of 1.0 kg in favor of the detemir group, with a minimum of 80% power testing at the 0.05 level of significance. The DiD effect size of 1.0 kg was supported by results of randomized head-to-head studies.[1-7] A sample size of 215 patients per group was estimated to have 80% power to detect a 1.0-kg DiD in mean weight change between insulin groups.

Covariate analysis. Measured covariates included baseline BMI, age, gender, concurrent medications, baseline HbA_{1c} value, prescriber, final insulin dose, and comorbidities. Baseline characteristics were summarized by insulin treatment group with means (for continuous measures) and percentages (for categorical measures) to evaluate the potential for selection bias. The primary endpoint of interest for each insulin group was the greatest change in total body weight. A DiD in mean change in total body weight between the detemir and glargine groups was tested by the analysis of covariance (ANCOVA) method.[15] Change in total body weight was regressed on a binary predictor variable for insulin treatment (detemir vs glargine [reference]) with adjustment for covariates. Additionally, weight change associated with insulin type was regression-adjusted for each concurrent medication and composites of concurrent medications. Under the null hypothesis of no benefit from detemir treatment relative to glargine treatment, a significant detemir effect was defined as one for which the estimated effect was negative and the upper 1-sided 95% confidence interval (CI) did not include 0 kg, and a statistically significant effect for the magnitude of weight-saving effect was one for which the estimated effect wasnegative and the CI did not include –1 kg.

To identify which patient subgroups experienced the greatest or least weight change, multivariate analysis was applied to collected covariates (age, gender, race, pre- and postexposure BMI and HbA_{1c} values, concurrent comorbidities, concurrent medications, and beginning and final insulin doses).

All statistical analyses were conducted using the most current version of the R statistical software (R Foundation for Statistical Computing, Vienna, Austria).

Results

There were 2,531 patients who received treatment with one of the 2 study insulins (1,593 received glargine and 938 received detemir) within the EMR data set. One hundred nine patient records (56 of glargine users and 53 of detemir users) met all screening criteria and underwent full abstraction. After screening of the entire list of patients who received study insulins, the planned sample estimates for the primary outcome were not met. However, the observed effect size of the primary outcome was larger than the estimate in the sampling calculations, resulting in adequate power to test the primary hypothesis. Significantly more patients in the glargine group were insured ($P = 0.0171$). There were no other statistical differences in baseline characteristics between the insulin groups (Table 1).

The unadjusted mean (SD) changes in body weight associated with detemir and glargine use were 0.86 (4.6) kg and 1.5 (4.2) kg, respectively (DiD, –0.64 kg in favor of detemir; $P = 0.45$). The ANCOVA model for change in body weight consisted of baseline body weight, mean insulin dose per kilogram of baseline body weight, days between baseline weight measurements, and concurrent sulfonylurea use (Table 2).

The covariate-adjusted DiD for estimated mean change in body weight associated with detemir use relative to glargine use was –1.5 kg ($P = 0.04$) in favor of detemir (Table 3, Figure 1). In the covariate-adjusted model for change in HbA1c level, the mean change in HbA1c was lower for both groups, but the reduction was greater for the detemir group by an absolute 0.57% ($P = 0.16$).

Discussion

Among all types of insulin, detemir insulin has been consistently demonstrated to be associated with the least weight gain in comparative randomized control studies. Our results further substantiate these findings and highlight that the reduced weight gain with detemir insulin occurs even in real-world practice settings, outside the intensity and scrutiny of controlled trials. The degree of weight gain reduction observed in the detemir group, after adjustments for covariates, was almost identical to reductions reported in previously published literature. The question of whether the magnitude of weight gain reductions experienced by detemir users is clinically significant remains unanswered by our study. The average baseline weight of subjects in the detemir group (Table 1) was 99 kg, suggesting that the average weight sparing experienced by detemir users represented a change from baseline in total body weight of only 1.5%. Weight change of this magnitude is generally not considered clinically significant in obese patients with type 2 diabetes. Rather, total body weight changes of 3% to 5% are generally regarded as the benchmark for clinical significance because of corresponding meaningful changes in triglycerides, low-density lipoprotein, blood pressure, insulin resistance, and need for medications.[13,16,17] The standard deviation and CI indicate that some patients in our study experienced weight sparing that may be deemed clinically significant.

Table 1. Baseline Patient Characteristics by Insulin Type

	Detemir (*n* = 53)	Glargine (*n* = 56)	*P* value
Age, mean (SD), y	53.0 (9.6)	54.7 (10.0)	0.39
Female, No. (%)	28 (53)	28 (50)	0.99
Race/ethnicity, No. (%)			
White	21 (40)	30 (54)	0.2624
Black	0	0	
Hispanic	27 (51)	20 (36)	0.3817
Asian/Pacific Islander	1 (2)	0	0.99
Other or unknown	4 (7)	5 (11)	0.99
Insurance status, No. (%)			
Insured	21 (40)	36 (64)	0.0171
Private (commercial)	6 (11)	10 (18)	0.4883
Medicaid	2 (4)	11 (20)	0.0239
Medicare	9 (17)	10 (18)	>0.99
Medicare and Medicaid	4 (7)	5 (9)	>0.99
Baseline weight, mean (SD), kg	99.6 (23.6)	99.7 (25.3)	0.98
Baseline BMI, mean (SD)	36 (7.4)	36 (8.4)	0.97
BMI >30, No. (%)	42 (79)	40 (71)	0.99
BMI >40, No. (%)	13 (24)	12 (21)	0.99
Initial insulin dose, mean (SD), units	15 (6.5)	16 (15.0)	0.66
HbA_{1c} concentration, mean (SD), %	10.0 (2.0)	9.8 (1.7)	0.09
Comorbidities, No. (%)			
Cardiovascular disease	4 (7)	10 (18)	0.1796
Smoking	19 (36)	23 (41)	0.644
Morbid obesity	13 (24)	12 (21)	0.99
Cerebrovascular disease	1 (2)	3 (5)	0.625
Depression	17 (32)	15 (27)	0.8601
Concurrent medication(s) for diabetes, No. (%)			
Metformin	46 (87)	45 (80)	0.99
Sulfonylurea	29 (55)	31 (55)	0.8974
Thiazolidinedione	2 (4)	2 (4)	0.99
DPP4 inhibitor	7 (13)	3 (5)	0.3438
GLP-1 agonist	1 (2)	2 (4)	0.99
Alpha-glucosidase inhibitor	0	1 (2)	0.99
Concurrent weight loss medication, No. (%)[a]	1 (2)	1 (2)	0.99
Concurrent weight gain medication, No. (%)[b]	38 (72)	37 (66)	0.99

[a]Other prescribed medication types associated with weight loss included the following: orlistat, phentermine product, sibutramine, and topiramate product.
[b]Other prescribed medication types associated with weight gain included the following: tricyclic antidepressant, atypical antipsychotic, and lithium.

This finding is similar to findings of Raskin et al,[4] who described detemir users who had weight savings of as much as 2.19 kg, and Elisha et al,[5] who reported weight savings of as much as a 3.6 kg with detemir use. Neither of these studies provided sufficient detail to determine the frequency at which patients experienced clinically

Table 2. Results of ANCOVA Modeling With Adjustments for Mean Change In Body Weight

Covariate	Adjustment (Regression Coefficient)	95% CI
Baseline weight	–0.023 kg per 1 kg of baseline weight	–0.05 to 0.001 ($P = 0.13$)
Mean insulin dose	7.1 kg per 1-unit increase	4.98-10.37 ($P < 0.001$)
Days between measurements	0.0059 kg per day	–0.001 to 0.014 ($P = 0.13$)
Concurrent sulfonylurea	2.6 kg	1.25-4.01 ($P < 0.001$)

Abbreviations: ANCOVA, analysis of covariance; CI, confidence interval.

Table 3. Crude and Covariate-Adjusted DiD Estimates for Weight Change[a]

	Baseline Weight, kg	Days Between Weight Measurements	Weight at Study Endpoint, kg	Weight Change	Unadjusted DiD Estimate, kg	Adjusted DiD Estimate
Detemir group ($n = 56$)	99.6 (23.6)	201 (98)	100.5 (22.6)	0.86 (4.6)	–0.64 (95% CI, –2.29 to 1.00; $P = 0.45$)	–1.50 (95% CI, –2.89 to –0.12; $P = 0.04$)
Glargine group ($n = 53$)	99.7 (25.3)	186 (96)	101.2 (25.0)	1.5 (4.2)	[Reference]	[Reference]

Abbreviation: CI, confidence interval; DiD, difference-in-differences.
[a]All data are mean (standard deviation) unless specified otherwise.

significant weight gain or which patient subgroups experienced the greatest or least weight gain.

Our study had several limitations. First, retrospective chart reviews inherently threaten internal validity because of the reliance on medical care documentation, lack of randomization, and interrater variance during abstraction of records. We attempted to minimize variability by using strict inclusion criteria to define healthcare exposure and documentation requirements for the primary endpoint of interest. Covariate analysis methodology was used in an attempt to account for confounders and modifiers introduced by use of a nonrandomized data set. To improve interrater reliability, standardized and rigorous abstraction protocols were used, abstractors were blinded to the study hypothesis, and ICC tests were used for quality audits. Second, because the study was limited to a single health system, further research is required to assess the broad-scale generalizability of our findings. Third, the majority of potential subjects were excluded because of missing data within the health record, and more exclusions occurred in the glargine user group. Eliminating these cases from analysis may have introduced a hidden bias, which could have influenced the primary endpoint of the study, although it is possible that missing data were randomly absent.

Accepted mechanisms of weight gain during insulin therapy include hypoglycemic defensive snacking, caloric retention from reduced urinary excretion of glucose, and the general anabolic effects of insulin. Additionally, when insulin is given subcutaneously there is a greater degree of peripheral glucose uptake (PGU) and a reduction in endogenous glucose production (EGP) compared to physiologic insulin release. Under normal physiologic conditions, insulin is released into the portal vein and arrives at the liver, where it suppresses EGP. Only 40% to 50% of endogenous insulin actually reaches the systemic circulation, where it acts on peripheral muscle and fat to increase PGU and suppress lipolysis. Subcutaneously administered insulin avoids first-pass metabolism, producing greater PGU and reduced EGP, both of which would be expected to promote weight gain.[11]

Detemir and glargine have a significant weight-sparing advantage over older basal insulin preparations, likely because both formulations exhibit improved predictability in absorption and action, resulting in less hypoglycemia and subsequent defensive snacking.[11,18] Detemir's weight-sparing advantage over glargine is poorly understood but thought to be related to its more similar pharmacokinetic and pharmacodynamic parity with physiologic insulin tissue distribution and hepatic effects. Detemir is an insulin analogue that is acylated with a fatty acid that reversibly binds with albumin and is 98% bound to plasma albumin. The high degree of protein binding in circulation reduces peripheral exposure (and PGU) while retaining hepatic effects (eg, EGP). Thus, detemir's relative balance between hepatic and peripheral actions may resemble physiologic insulin

effects more closely than glargine actions.[11,19]

Conclusion

After adjustments for covariates, the mean weight gain associated with detemir use was significantly less than that with glargine use, and the magnitude of weight sparing was consistent with weight sparing demonstrated in randomized controlled trials. These results further substantiate detemir's weight-sparing properties in type 2 diabetes, even under conditions found in a real-world practice settings. The clinical significance of these findings is undetermined and requires further investigation. At the very least, the results of this study add to the growing body of knowledge about diabetes treatment and strategies to reduce insulin-associated weight gain.

Disclosures

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