Insulin Detemir Use Is Associated With Higher Occurrence of Hypoglycemia in Hospitalized Patients With Hypoalbuminemia

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The insulin analogs detemir and glargine are the two basal insulins commonly used in hospitalized patients (1). Their slow-release reservoir is different—serum albumin for detemir and subcutaneous microcrystals for glargine (2,3).

There is a common belief that detemir should be avoided in hypoalbuminemic patients because they have less predictable levels of free insulin, raising a concern for higher risk of hypoglycemia (4,5). Nevertheless, the guidelines recommend using either insulin with impartiality to hypoalbuminemia (1). There are no human studies on pharmacokinetics or outcomes of using detemir in hypoalbuminemic patients. Randomized controlled studies of detemir versus glargine have not found a difference in hypoglycemia (6–9), but these trials included only a few hundred patients who probably were not hypoalbuminemic. A recent retrospective study found a higher rate of hypoglycemia (<70 mg/dL) in detemir-treated compared with glargine-treated inpatients (10).

We took advantage of the large Rambam Health Care Campus inpatient database to retrospectively compare hypoglycemia in inpatients with low albumin treated with detemir or glargine. Data were retrieved using MDClone (mdclone.com), a query tool that provides comprehensive patient-level data of wide-ranging variables in a defined time frame around an index event. The study was approved by the Rambam Institutional Review Board.

Data were collected for all patients over 18 years old hospitalized between 1 February 2012 and 31 December 2016, treated with detemir or glargine, and with at least one hospitalization albumin blood test. The date of lowest albumin level was set as the index event. Exclusion criteria were "obstetric ward" (where glargine is not used) and glucose <15 mg/dL or albumin <1 g/dL (owing to the scarcity of such events). The time frame for hypoglycemia was defined as 5 days around the index event (2 days before and 2 days after).

Patient variables extracted were demographics; hospitalization length; ward; relevant medications; and minimal, maximal, and standard deviation of albumin, creatinine (spectrophotometric autoanalyzer [Dimension; Siemens, IL]), and glucose (acquired by StatStrip central glucometer [Nova Biomedical] or the same spectrophotometric analyzer).

Glargine- or detemir-treated patients were first compared using simple bivariate analysis. Logarithmic transformation was applied for variables with a skewed distribution.

To assess the relationship between albumin, insulin glargine/detemir, and hypoglycemia, the following regression models were used. First, univariate regression coefficients measured associations between hypoglycemia and variables that impact hypoglycemia: age, sex, weight, insulin dose, home insulin before hospitalization, short-acting insulin during hospitalization, minimal albumin, maximal creatinine, admission length, and ward. Next, a forward and backward stepwise Akaike information criterion regression method was performed; the dependent variable was glucose ≤70 mg/dL. An identical logistic analysis was done for glucose ≤54 mg/dL. Last, a stepwise forward and backward regression method with second-order interactions was performed.

To further test the "common belief" regarding the effect of detemir on hypoglycemia risk in hypoalbuminemic patients, we used the stepwise regression model results. Independent variables were fixed using the mean (continuous variables) or highest frequency (categorical variables) in the cohort. Albumin levels were set between 1 and 4 g/dL in 0.1 intervals, and hypoglycemia risk was predicted using the above models.

Overall, 4,677 inpatients met inclusion criteria, 82.2% treated with glargine and 17.8% with detemir. Glargine-treated patients differed from detemir-treated patients in some baseline characteristics: they were older (67.2 ± 13.9 vs. 65.3 ± 13.6 years), had a higher male percentage (56.9% vs. 51.2%), had lower weight (84.3 ± 20.4 vs. 86.4 ± 20.5 kg), had a longer hospital stay (12.9 ± 17.2 vs. 11.4 ± 14.9 days) ($P < 0.05$), and had a lower minimal albumin measurement (2.6 ± 0.74 vs. 2.8 ± 0.7 g/dL) ($P < 0.0001$) but no difference in albumin variability.

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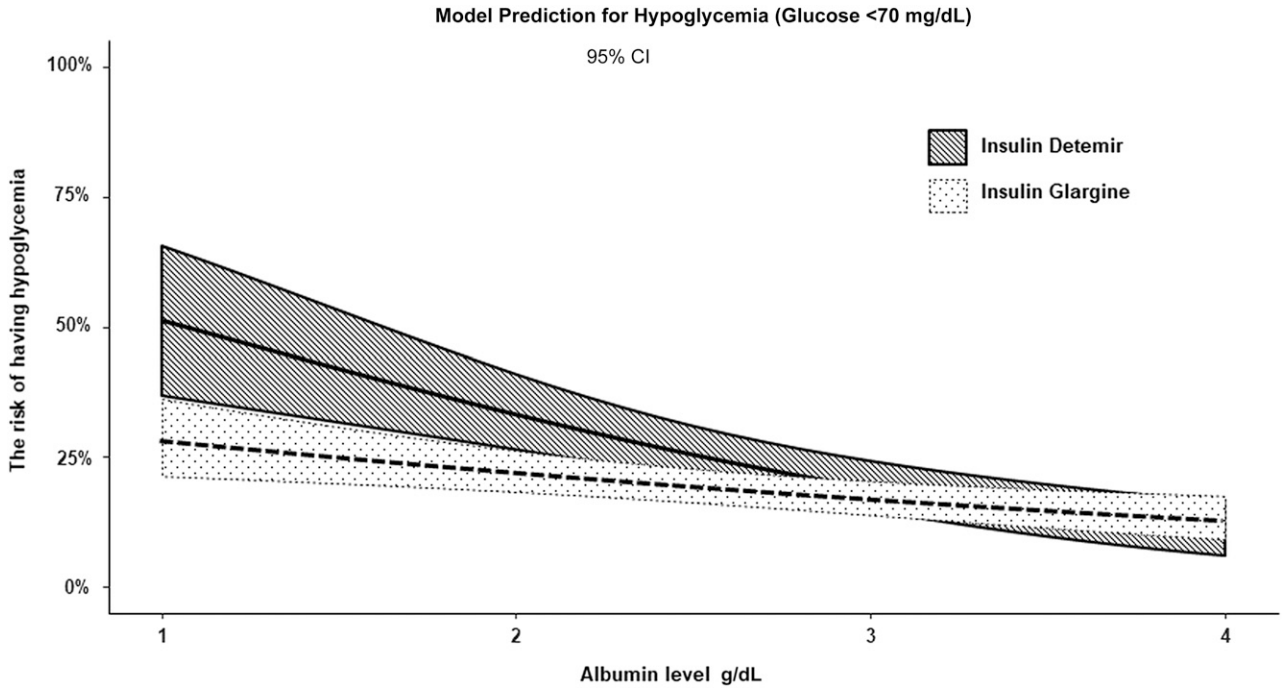

Figure 1—Illustration of logistic model for prediction of the risk for hypoglycemia according to albumin measurements. Model is based on fixed-profile patients with the following characteristics: age = 67 years, weight = 84 kg, creatinine = 1.6 mg/dL, basal insulin dose = 21 units, treated with insulin at home, hospitalized in an internal medical ward, length of stay = 12 days.

The rate of glucose <70 mg/dL was 16.8% under glargine and 20.9% under detemir ($P < 0.05$), and the rate of glucose <54 mg/dL was 6.3% under glargine and 8.4% under detemir ($P < 0.05$). Median and maximal glucose were slightly higher under glargine (191.3 ± 63.8 vs. 186.1 ± 62.2 mg/dL and 306.8 ± 114.1 vs. 296.4 ± 107.7 mg/dL, respectively; $P < 0.05$), and mean glucose was similar (198.7 ± 61.4 vs. 194.4 ± 60.2 mg/dL). Fewer glargine-treated patients were treated with insulin at home (51.3% vs. 66.5%), and more were treated in parallel with rapid-acting insulin (84.4% vs. 80.3%) ($P < 0.0001$). Glargine-treated patients had a lower basal insulin dose (20.8 ± 11.7 vs. 23.1 ± 13.3 units) ($P < 0.0001$), but there was no difference in units/kg ($P = 0.7$).

Univariate logistic regression analysis found that risk of hypoglycemia was associated with age, weight, length of stay, maximal creatinine, minimal albumin, home insulin treatment, basal insulin dose, and use of rapid insulin ($P < 0.005$). These variables were entered as possible predictors into the Akaike information criterion analysis. Treatment with detemir increased the odds for hypoglycemia by 35%. Home insulin increased hypoglycemia by 62%. Hospitalization in internal medicine increased hypoglycemia by 35% compared with all other wards, and each additional hospitalization day increased hypoglycemia by 15%. Minimal albumin level was negatively associated with hypoglycemia (odds ratio = 0.68, 95% CI 0.58–0.80) such that for 1 g/dL decrease in minimal albumin, hypoglycemia increased by 32%. Results for hypoglycemia at glucose <54 mg/dL were very similar.

The difference in albumin levels of glargine- versus detemir-treated inpatients demonstrates that physicians tend to avoid detemir in hypoalbuminemia. To evaluate the reliability of the "common belief" that detemir should be avoided in hypoalbuminemia, we evaluated the effect of albumin level and insulin type on hypoglycemia, while overcoming physicians' bias, by generating a multivariate model taking into account only albumin while fixing all other variables. This model is presented in Fig. 1, which illustrates that for individuals with low albumin, the risk for hypoglycemia under detemir treatment is significantly higher compared with glargine treatment, but for normal-range albumin, the same risk for hypoglycemia is present for the two insulins.

In conclusion, this retrospective analysis of a large database of hospitalized patients found that there is an excess risk for hypoglycemia in inpatients with hypoalbuminemia treated with detemir. This supports the long-held belief that insulin detemir levels are less predictable in hypoalbuminemia. On the other hand, there was no difference in occurrence of hypoglycemia between the two insulins in individuals with albumin over 3 g/dL, confirming the equivalent safety of both insulins in the majority of people.

The main limitations of this study are its retrospective design and the unavoidable differences between glargine and detemir groups. We made an effort to overcome these differences by using a multivariate model that corrects for all these differences.

The results suggest that it may be advisable to consider avoiding the use of detemir (and perhaps other albumin-bound insulins) in individuals with hypoalbuminemia.

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References

1. Umpierrez GE, Hellman R, Korytkowski MT, et al.; Endocrine Society. Management of hyperglycemia in hospitalized patients in non-critical care setting: an endocrine society clinical practice guideline. J Clin Endocrinol Metab 2012;97:16–38
2. Kurtzhals P. Engineering predictability and protraction in a basal insulin analogue: the pharmacology of insulin detemir. Int J Obes Relat Metab Disord 2004;28(Suppl. 2):S23–S28
3. Coppolino R, Coppolino S, Villari V. Study of the aggregation of insulin glargine by light scattering. J Pharm Sci 2006;95:1029–1034
4. Goldman-Levine JD, Lee KW. Insulin detemir—a new basal insulin analog. Ann Pharmacother 2005;39:502–507
5. Reilly JB, Berns JS. Selection and dosing of medications for management of diabetes in patients with advanced kidney disease. Semin Dial 2010;23:163–168
6. Swinnen SG, Dain MP, Aronson R, et al. A 24-week, randomized, treat-to-target trial comparing initiation of insulin glargine once-daily with insulin detemir twice-daily in patients with type 2 diabetes inadequately controlled on oral glucose-lowering drugs. Diabetes Care 2010;33:1176–1178
7. Raskin P, Gylvin T, Weng W, Chaykin L. Comparison of insulin detemir and insulin glargine using a basal-bolus regimen in a randomized, controlled clinical study in patients with type 2 diabetes. Diabetes Metab Res Rev 2009;25:542–548
8. Davis S, Friece C, Roderman N, Newcomer D, Castaneda E. Comparison of insulin detemir and insulin glargine for hospitalized patients on a basal-bolus protocol. Pharmacy (Basel) 2017;5:22
9. Zhang T, Lin M, Li W, et al. Comparison of the efficacy and safety of insulin detemir and insulin glargine in hospitalized patients with type 2 diabetes: a randomized crossover trial. Adv Ther 2016;33:178–185
10. Galindo RJ, David GM, Fayman M, et al. Comparison of efficacy and safety of glargine and determir insulin in the management of inpatient hyperglycemia and diabetes. Endocr Pract 2017;23:1059–1066