

Differential Effects of Adiposity on Pharmacodynamics of Basal Insulins NPH, Glargine, and Detemir in Type 2 Diabetes Mellitus

FRANCESCA PORCELLATI, MD, PHD
PAOLA LUCIDI, MD, PHD
PAOLO ROSSETTI, MD, PHD
PAOLA CANDELORO, PHD
ANNA MARINELLI ANDREOLI, MD

STEFANIA MARZOTTI, MD, PHD
PATRIZIA CIOLI, RD
GEREMIA B. BOLLI, MD
CARMINE G. FANELLI, MD, PHD

OBJECTIVE—To assess the role of adiposity on the pharmacodynamics of basal insulins NPH, detemir, and glargine in type 2 diabetes mellitus (T2DM), as estimated by glucose infusion rate (GIR) and endogenous glucose production (EGP) rate in the euglycemic clamp.

RESEARCH DESIGN AND METHODS—We examined the variables that best predicted GIR and EGP in 32-h clamp studies after treatment with subcutaneous injection of 0.4 units/kg NPH, detemir, and glargine in 18 T2DM subjects (crossover).

RESULTS—A multiple regression analysis revealed that BMI best predicted GIR variation during the clamp. BMI was inversely correlated with GIR in all three insulin treatments, but was statistically significant in detemir treatment only. BMI correlated positively with residual suppression of EGP in detemir, but not with glargine and NPH treatments.

CONCLUSIONS—Adiposity blunts the pharmacodynamics of all basal insulins in T2DM. However, as adiposity increases, the effect of detemir is lower versus NPH and glargine.

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We have shown that the pharmacokinetics and pharmacodynamics (PD) of basal insulins NPH, detemir, and glargine, when examined (euglycemic clamp), differ in subjects with type 2 diabetes mellitus (T2DM) (1). The primary PD end point parameter, the glucose infusion rate (GIR) over the 32 h of clamp study, was greater with glargine versus NPH and detemir.

We carried out the present analysis to determine the independent variable(s) that best predicted the PD insulin effect, as measured by GIR in clamp studies, after treatments with basal insulins NPH, detemir, and glargine.

RESEARCH DESIGN AND METHODS

After approval by the local ethical committee and informed written consent, 18 T2DM subjects on insulin and/or oral hypoglycemic agents were recruited (Supplementary Table 1) and studied (1).

Stepwise regression analyses were done to identify independent variables that best predicted GIR response. As a set of independent variables, we obtained the age of patients, duration of diabetes, plasma C-peptide, and BMI, which we included in the multiple regression analysis. GIR was the dependent variable. Pearson product moment correlation was used to assess

association between changes in GIR and other parameters. Data were analyzed by a mixed-model analysis including sequence, treatment, and BMI (<29 and >29 kg/m², i.e., below and above the median BMI of the overall group) as fixed factors and patients (nested within sequence) as a random effect followed by Bonferroni adjustments for multiple comparisons. Data in the text were expressed as means ± SD and as means ± SE in Fig. 1. All tests were two-sided tests with a nominal significance level of 0.05. Statistical analysis was performed using NCSS 2007 (NCSS, LLC, Kaysville, UT, www.ncss.com).

RESULTS—A multiple regression analysis revealed a significant model ($F_{4,13} = 4.44$, $P = 0.017$; adjusted $R^2 = 0.45$). The significant predictor variable was BMI (standardized coefficient = -0.575), which accounted for 39% of variation in GIR variable ($P = 0.013$) (Supplementary Tables 2 and 3). Bivariate correlations of BMI and GIR split by treatment showed an inverse correlation that was significant only with detemir ($r = -0.68$, $P = 0.003$), but not with glargine ($r = -0.41$, $P = 0.11$) and NPH ($r = -0.37$, $P = 0.15$) (Supplementary Fig. 1). In addition, a positive and significant correlation was found between BMI and residual endogenous glucose production (EGP) with NPH and detemir ($r = 0.66$, $P = 0.005$, and $r = 0.62$, $P = 0.006$, respectively) but not with glargine ($r = 0.35$, $P = 0.17$) (Supplementary Fig. 1). An inverse and significant association with duration of action was found for NPH and detemir but not for glargine (Supplementary Table 4).

On the basis of BMI status, with all three basal insulins, GIR was lower in people with BMI >29 kg/m² compared with people with BMI <29 kg/m² (Fig. 1), but statistical significance was achieved with detemir treatment only (598 ± 604 and $1,564 \pm 649$ mg/kg, respectively; $P = 0.03$) and not with NPH ($1,058 \pm 859$ and $1,282 \pm 532$ mg/kg) and glargine ($1,408 \pm 563$ and $1,668 \pm 807$ mg/kg) (both $P > 0.2$). In addition,

From the Department of Internal Medicine, Section of Internal Medicine, Endocrinology and Metabolism, University of Perugia, Perugia, Italy.

Corresponding author: Geremia B. Bolli, gbolli@unipg.it.

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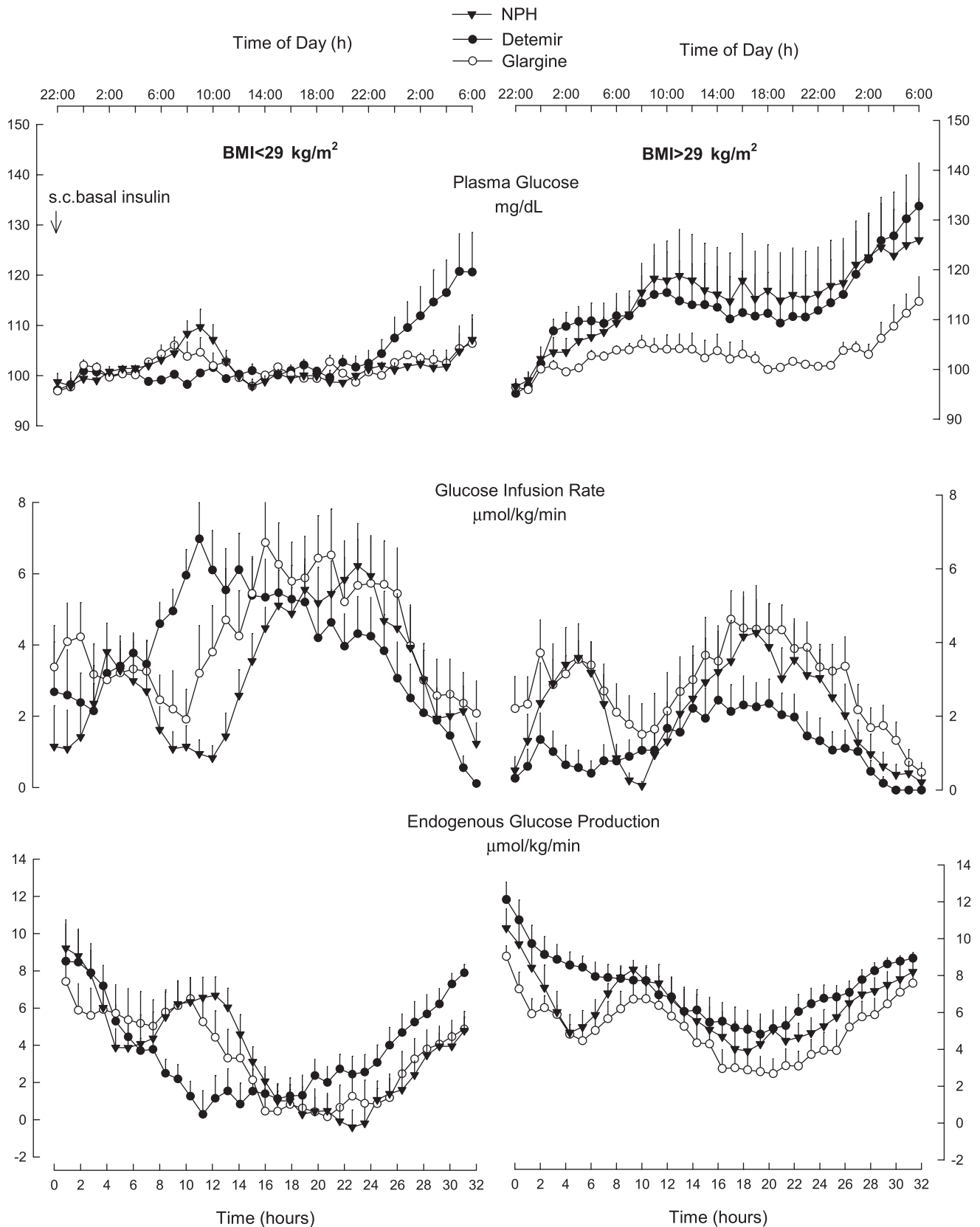


Figure 1—Plasma glucose, rates of glucose infusion to maintain euglycemia, and endogenous glucose production in 18 subjects with T2DM given subcutaneous (s.c.) injection of basal insulin NPH or detemir or glargine (1). Left panels: nine subjects with BMI <29 kg/m²; right panels, nine subjects with BMI >29 kg/m².

residual EGP was greater in people with BMI >29 vs. <29 kg/m², although significance was achieved with detemir (7.8 ± 1.8 vs. 4.1 ± 2.1 μmol/kg/min, *P* = 0.001) but not with glargine (5.3 ± 1.3 vs. 3.8 ± 2.7 μmol/kg/min, *P* = 0.231) and tended to be different with NPH (6.6 ± 2.2 vs. 4.0 ± 2.1 μmol/kg/min, *P* = 0.068).

CONCLUSIONS—In the euglycemic clamp during intravenous infusion of regular insulin, there is an inverse correlation between BMI and GIR in T2DM (2), indicating that the greater the adiposity, the lower the insulin sensitivity. It is reasonable to translate this information to the clinical situation of the subcutaneous injected long-acting insulin, but no study so far has examined the question directly.

We recently reported that GIR area under the curve (AUC)_{0–32 h} (a measure of insulin effect on glucose metabolism after subcutaneous injection of long-acting insulins) is greater with glargine than with NPH and detemir (1). However, in that study (1), the factor(s) responsible for GIR variations between T2DM subjects and between the three basal insulins were not assessed.

The results of the present analysis indicate that BMI is a factor that may well predict the PD of basal insulins NPH, detemir, and glargine, as indicated by the inverse correlation between BMI and PD (GIR AUC_{0–32 h}). In addition, the results indicate that the PD of the three basal insulins is differentially affected by BMI (i.e., at increasing BMI, the PD was lower for detemir than for NPH and glargine). Likewise, EGP, the well-known primary determinant of fasting blood glucose (3), was more suppressed by glargine and NPH compared with detemir in people with greater BMI. Although all three basal insulins showed a lower suppression of EGP for increasing BMI, the correlations were significant only for NPH and detemir, suggesting that glargine has a greater effect in restraining EGP at increasing adiposity. The reasons for the lower effect of detemir at higher BMI are unclear. We acknowledge that these conclusions have limitations because of the small sample size of the study; nevertheless, the results might explain findings of recent clinical studies.

A previous crossover study, longer than 2 months, reported higher dose requirements of the long-acting insulin analogs compared with NPH insulin,

in a group (*n* = 20) of T2DM subjects with BMI >30 kg/m² (4). Results of studies examining larger groups of T2DM subjects for ≥6 months indicated that higher detemir insulin doses are required versus NPH (5) and glargine for similar efficacy on glycemic control (6–9). However, none of those studies ascertained the impact of BMI on insulin dose requirements. A recent post hoc analysis (10) of a study comparing insulin glargine (once a day) and detemir (twice a day) in T2DM (9) titrated to reach similar glycemic control has shown that the higher dose of insulin detemir needed was directly correlated with BMI (10).

In conclusion, BMI largely explains the PD effect of insulins NPH, detemir, and glargine in T2DM subjects previously reported (1). In fact, as BMI increases, the effect of detemir is lower versus NPH and glargine (lower GIR and greater EGP). The current study suggests that it is obesity that primarily drives the larger detemir versus NPH and glargine doses needed in T2DM.

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F.P. wrote the study protocol, performed clamps, researched data, and reviewed and edited the manuscript. P.L. performed clamps and glucose turnover measurements, analyzed data, and reviewed and edited the manuscript. P.R. enrolled patients, performed clamps, researched data, and reviewed and edited the manuscript. P.Ca. performed clamps and laboratory assays and reviewed and edited the manuscript. A.M.A., S.M., and P.Ci. performed clamps and reviewed and edited the manuscript. G.B.B. provided the study concept and design, supervised the protocol development and the research, contributed to discussion, and reviewed and edited the manuscript. C.G.F. performed clamps, analyzed data, performed statistical analysis, and wrote the manuscript.

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