Low Levels of Unmodified Insulin Glargine in Plasma of People With Type 2 Diabetes Requiring High Doses of Basal Insulin

Paola Lucidi,[1] Francesca Porcellati,[1] Hannele Yki-Järvinen,[2] Matthew C. Riddle,[3] Paola Candeloro,[1] Anna Marinelli Andreoli,[1] Geremia B. Bolli,[1] and Carmine G. Fanelli[1]

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Glargine metabolism has been studied in insulin-treated people with type 2 diabetes (T2D) at usual glargine doses of 0.4–0.8 units/kg/day (1,2). In some obese subjects with insulin-resistant T2D, higher basal insulin doses are needed, and the question of safety of glargine (3) is therefore still relevant. Epidemiological studies indicate that the risk of cancer is especially elevated in obese individuals with insulin-resistant diabetes requiring high insulin doses (4). Unmodified insulin glargine has been suggested to confer a higher risk of cancer (3), but prior studies have shown that, at usual doses, an active metabolite (M1) with actions similar to human insulin is the main circulating molecule after glargine injection (1,2).

The aim of the current study was to establish the plasma levels of insulin glargine (M0) and its metabolites M1 and M2 (1,2) in subjects with T2D treated long-term with glargine dose ≥1.2 units/kg/day.

Blood samples of 10 subjects with T2D (male/female 5/5, age 56 ± 10 years, BMI 37.9 ± 7.9 kg/m^2, A1C 8.9 ± 1.3% [74 ± 15 mmol/mol], diabetes duration 19 ± 10 years, glargine dose 162 ± 63 units/day [1.49 ± 0.28 units/kg/day], prandial insulin dose 74 ± 37 units/day) (mean ± SD) were drawn in the fasting state, 12 ± 1 h after last subcutaneous glargine injection and processed as previously described (1,2). Plasma was stored at −80°C and analyzed within 6 months (to prevent possible deterioration) for M0, M1, and M2 (liquid chromatography–tandem mass spectrometry method, sensitivity 0.2 ng/mL for each analyte, ~34 pmol/L) (for method details see ref. 2).

Plasma M0 was 31 ± 41.6 pmol/L, whereas M1 concentration was 457 ± 337 pmol/L in the 10 subjects studied. M0 represented 4.1 ± 6.1% and M1 represented 95.9 ± 6.1% of total plasma insulin. M2 was not detected in any of the subjects studied.

Plasma M0 was detected in only 4 out of the 10 subjects, whereas M1 was detectable in all 10 subjects (Fig. 1). In the 4 subjects in whom it was detectable, M0 had a concentration of 78 ± 19 pmol/L (subject 1, 53 pmol/L; subject 3, 96 pmol/L; subject 6, 89 pmol/L; subject 10, 74 pmol/L) (Fig. 1) and represented 10.4 ± 5.2% of the total circulating insulin. M1 had a concentration of 772 ± 321 pmol/L in the 4 subjects in whom M0 was detected and represented 89.6 ± 5.2% of total circulating insulin.

Study limitations are the sample size and only a single blood sample examined 12 ± 1 h after last glargine dosing, which expresses metabolism of glargine in a steady-state condition (2). The results are consistent with previous observations at lower glargine doses (≤0.8 units/kg) in which sampling at 12 h could still, in some cases, detect glargine (M0) in plasma (1,2). A previous study in T2D on high glargine doses failed to detect M0, but samples were determined only >6 years after storage of blood samples drawn and processed under unspecified conditions, likely not suitable to preserve M0 (5). In the current study, we found that, even at high doses of insulin glargine, M0 (glargine) represented only 10% of total insulin concentration and was detectable only in 40% of individuals and at a concentration no higher than 100 pmol/L. These results suggest that insulin glargine treatment does not confer a greater risk of cancer as compared with human insulin in people with T2D who require very high insulin doses and are at high cancer risk (4).

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[1]*Department of Medicine, Perugia University School of Medicine, Perugia, Italy*
[2]*Department of Medicine, University of Helsinki, Helsinki, Finland*
[3]*Division of Endocrinology, Diabetes and Clinical Nutrition, Oregon Health & Science University, Portland, OR*

Corresponding author: Geremia B. Bolli, geremia.bolli@unipg.it.

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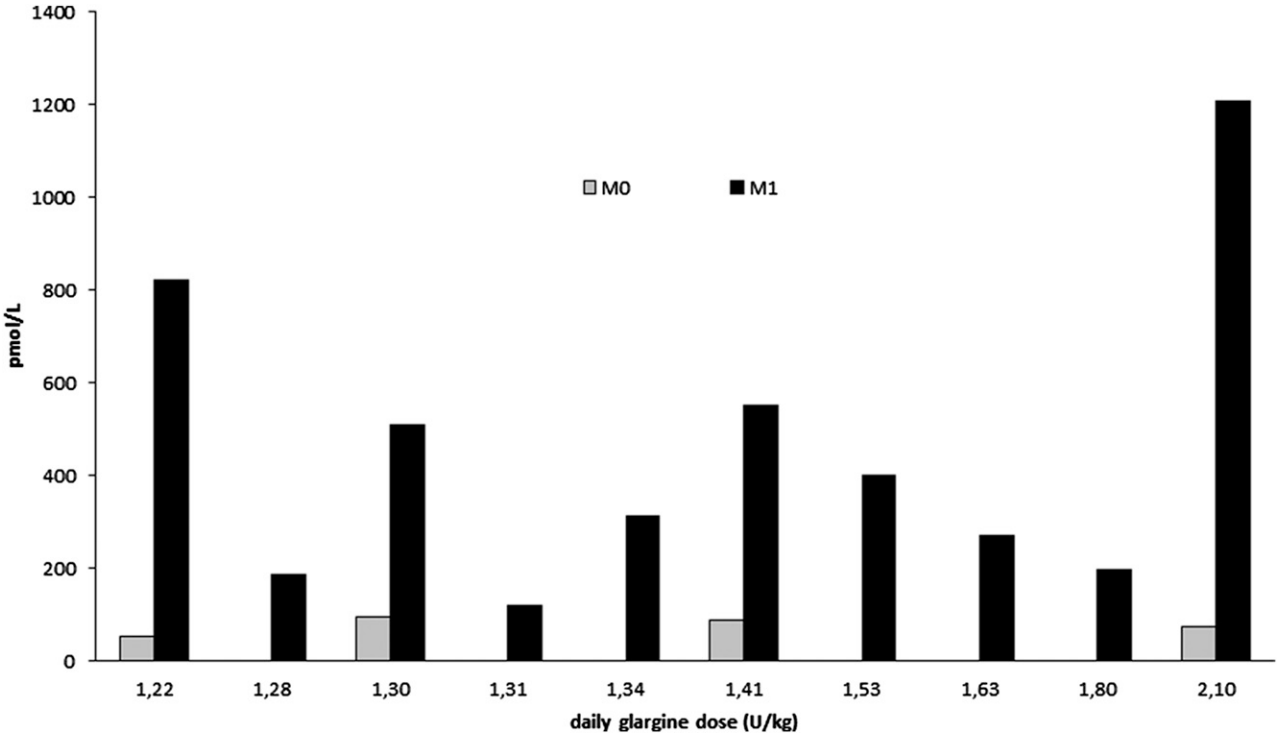

Figure 1—Plasma concentrations of M0 and M1 in the individual subjects with T2D, presented in order of increase in insulin dose required (units/kg/day).

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Author Contributions. P.L. enrolled patients, analyzed all data, and reviewed and edited the manuscript. F.P., H.Y.-J., M.C.R., and A.M.A. enrolled patients and reviewed and edited the manuscript. P.C. processed samples, performed laboratory assays, and reviewed and edited the manuscript. G.B.B. wrote the manuscript, provided the study concept and design, and supervised the research protocol and organization. C.G.F. enrolled patients, analyzed data, performed statistical analysis, and reviewed and edited the manuscript. P.L. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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