Titrating Beyond Glycemic Goal: "Post-Glycemic Target Phenomenon"

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In clinical trials in which once-daily basal insulin is titrated to fasting plasma glucose (FPG) targets, the goal is usually reached before the end of the study. After reaching the goal but before the end of the study and if the titration is continued, the mean dosage rises, but without a change in the mean FPG.[1] We had the opportunity to observe this "post-glycemic goal phenomenon" in a group of subjects with uncontrolled type 2 diabetes titrated with once-nightly insulin determir.

For 12 weeks, insulin was titrated 3 U either upward or downward every 3 days to achieve and maintained a mean 3-day FPG of 80–110 mg/dl. Self-titration was reinforced and hypoglycemia assessed by weekly phone calls and clinic visits every 4 weeks.

Fifteen subjects were observed for ≥28 days during this period of the post-glycemic goal phenomenon. The dosage increased from 50.7 to 68.1 U (p = .001) despite an actual increase in FPG, 97 ± 11 to 105 ± 29 mg/dl, respectively (p = .109). The individual subject's daily FPG standard deviation varied widely, ±6.4 to ±46.2 mg/dl, and correlated with the individual's dosage increase (r = 0.623; p < .01) and with the individual's FPG standard deviation during the first 3 days after insulin initiation (r = 0.838; p < .001). An example of two subjects' daily FPG following attainment of goal is shown in **Figure 1**. There was no mean weight gain during the 28 days, and only one subject had more frequent hypoglycemia than the period before the goal was reached.

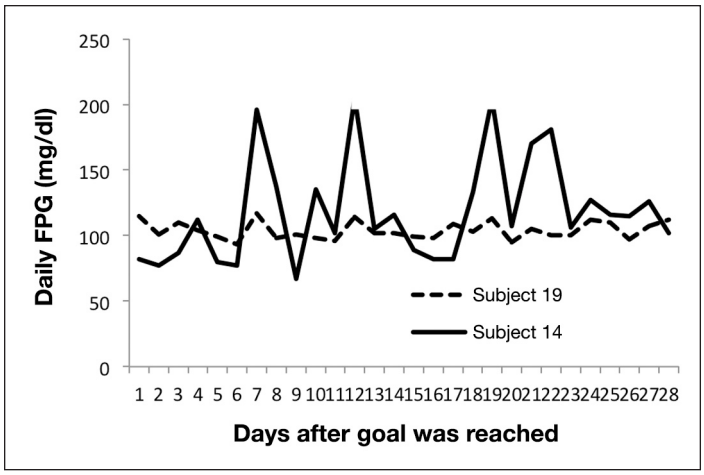

Figure 1. A comparison of daily FPG of two subjects during the 28-day period after initially achieving a mean 3-day FPG of <110 mg/dl. The broken curve is that of subject 19 who did not require a change in their dosage during this period, and the solid curve is subject 14 who had the greatest increase in dosage, 53 U, during this period.

Qu and coauthors[2] have reported that day-to-day FPG variability (coefficient of variation) from the 12th week to the end of their 24-week study and upon initiation of insulin were correlated to the incidence of hypoglycemia during the 12–24-week period. Our observations suggest that FPG variability is also associated with the post-goal dosage increase. Our failure to observe weight gain and increased hypoglycemia could be from our small sample size. Progressive beta-cell failure could not explain dosage increases because the observation period was only 28 days. Since there was none, weight gain was not responsible for increasing insulin resistance.

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As in our study, the glycemic goal dosage is not fixed but changes during titration, and the average dose is driven, in part, by those subjects with wide FPG variability. The variability leads to increased hypoglycemia[2] and probably excessive dosage, as suggested by our observations. Larger studies may find an association between variability and weight increase.

If irregular nightly eating is a major influence on FPG variability, then the basal dose should be titrated under conditions of a structured diet. Since high-FPG-variability individuals may be identified upon insulin initiation, as shown by both Qu and coauthors[2] and our study, early detection and correction of the causative factors may lead to lower basal insulin doses, hypoglycemia rate, and weight gain.

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