Comment on: Gögebakan et al. Glucose-Dependent Insulinotropic Polypeptide Reduces Fat-Specific Expression and Activity of 11β-Hydroxysteroid Dehydrogenase Type 1 and Inhibits Release of Free Fatty Acids. Diabetes 2012;61:292–300

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Gögebakan et al. (1) suggest that glucose-dependent insulinotropic polypeptide (GIP) inhibits free fatty acid (FFA) release via direct insulin-independent effects. Their in vitro data are accompanied by a clinical study in which 11 obese male subjects were studied during two (blinded?) 240-min intravenous infusions with GIP (2 pmol/kg/min) and saline, respectively. Because insulin is a well-known suppressor of circulating FFAs, one of the challenges that Gögebakan et al. encounter is to differentiate between the effect of GIP per se and any indirect effects of GIP (in particular via insulin) as outlined by Asmar et al. (2,3). Gögebakan et al. state that the trial was performed under euglycemic and normoinsulinemic conditions. However, in sharp contrast to results obtained using similar study designs (3,4) and despite GIP's well-described insulinotropic effect even at fasting plasma glucose levels (3–5), the investigators found a clear rise in serum insulin during the saline infusion and a flat-line insulin response during the GIP infusion. This difference was mirrored in a reduction of plasma glucose during the "insulinotropic" saline infusion. Although these data favor the idea that any effects of GIP on circulating FFA levels would be mediated directly (at least not via increased insulin), the surprising results on insulin and glucose are disturbing.

In the article by Gögebakan et al., most results are depicted as baseline-subtracted data—no good reason for this is given—and apparently, the statistical analyses have been carried out based on these data. This may constitute a serious problem for the interpretation of the results. When subtracting baseline results, it is of importance that variation of these has been minimized (e.g., by averaging multiple baseline measurements) in order to avoid transferring a single aberrant value to a systematic error in the entire dataset; Gögebakan et al. have only one baseline measurement, it is not stated whether samples from the two study days were assayed in a mixed fashion, and the interassay and intra-assay coefficients of variation of their FFA assay are not reported. Scrutinizing the absolute FFA data (reported in the text) it becomes clear that the baseline values during the two study days are different. This difference seems to be the only statistically significant difference in the three time-point FFA dataset (it is mentioned that FFAs were also determined at other time points, but these results are not reported). Thus, a rather distinct and unexpected rise in FFA during the placebo infusion contributes to the observed difference. Nevertheless, the authors state that "…FFAs were significantly and time-dependently reduced during GIP infusion compared with baseline and compared with saline infusion…" (but at the same time report a *P* value of 0.32 for treatment vs. time interaction for the absolute FFA values).

In conclusion, *1*) the surprising insulin and glucose results reported by Gögebakan et al. are unaccounted for; *2*) subtraction of baseline values is problematic—especially when these differ dramatically and/or minimization of variation is not accounted for; and *3*) the reported effect of GIP on FFA levels seems rooted in low baseline FFA levels during the saline infusion day.

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