Mennier's hypothesis revisited: postprandial (PPG) vs fasting (FPG) hyperglycemia at baseline and response to basal or premixed insulin stratified by HbA1c target achieved

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Background and aims: Mennier's cross-sectional study in Type 2 Diabetes (T2D), using 4-point glycaemic profiles during daytime, showed a greater contribution of PPG vs FPG to overall hyperglycaemia at lower HbA1c. We challenged this hypothesis, using a 24h glycaemic profile and comparing effect of a basal insulin, insulin glargine (G; n=1014) with a premix insulin with a prandial component, insulin lispro mix 25 (LM25; n=1045).

Materials and methods: In the initiation phase of DURABLE study [T2D on ≥2 OADs], patients were randomized to once-daily G or twice daily LM25 for 24 weeks. Relative 24h contributions of PPG and FPG to overall hyperglycaemia were calculated from 7-point glucose profiles with Area Under the Curve (AUC) for FPG between 100 mg/dL and fasting glycaemia and for PPG above the line projected from fasting glycaemia.

Results: At baseline, with increasing HbA1c, contributions of PPG to total AUC increased from 59 to 73% and FPG decreased from 41 to 27% (Figure 1). FPG AUC increased linearly with HbA1c, while PPG AUC increased only slightly. At endpoint, both LM25 and G lowered PPG AUC but only LM25 lowered FPG AUC. Below 8% and between 8-9% HbA1c at baseline, LM25 allowed a significantly higher % of patients to reach target <7% HbA1c vs G (72 vs 62% and 52 vs 43%, respectively). Similar % of patients reached target HbA1c with LM25 and G in quartiles HbA1c 9-10% (31 vs 28%) and ≥10% (28 vs 25%). Comparison of patients reaching target, or not, per quartile, showed baseline HbA1c. FPG and PPG AUC were similar but decreases were greater in those reaching target, allowing lower endpoint values. The higher the HbA1c baseline quartile, the greater was the absolute decrease in HbA1c for both insulins. Patients with baseline HbA1c <8%, not reaching target with both insulins, had a higher % of PPG AUC at baseline (~49 vs ~37%), suggesting they could benefit from an insulin regimen with a higher prandial percentage or higher insulin doses. Patients not reaching target had a slightly higher insulin dose but lower rate of hypoglycaemia, suggesting insulin resistance, and possibly, an unwillingness to increase dose further and/or poor compliance to lifestyle and the insulin regimen.

Conclusions: At baseline, the relative contribution of PPG vs FPG decreased with higher HbA1c, confirming Mennier's findings, and with a relevant role of PPG only at lower HbA1c and hence a higher % of patients reaching target with LM25 at low HbA1c quartiles. However, PPG AUC predominated at all HbA1c quartiles and was potentially amenable to further improvements. In all HbA1c quartiles, there was a lower decrease in FPG and PPG AUC in patients above target, suggesting that insulin dose could be increased further or then patients need to be advanced to more intensive regimens.

Figure 1: AUC FPG vs. AUC PPG at Baseline for all Randomized Patients (N=2089)

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