Statistical Analysis of 8-Point Self Measured Capillary Glucose Profiles in Type 2 Diabetic Patients to Compare the Efficacy of Three Different Insulin Regimens

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Haemoglobin A1c (HbA1c) provides an integrated measure of glycaemic exposure over the preceding 2 to 3 months. It is the current gold standard for monitoring glycaemic control and is an established risk factor for future diabetes-related complications. HbA1c, however, does not provide data about within-day or day-to-day fluctuations in glucose levels that are used to inform changes in doses or types of antidiabetic therapy, to warn of impending hypoglycaemia and which may also have an impact on long term outcomes. This makes Self Measured Capillary Glucose (SMCG) profiles an important adjunct to HbA1c because they can distinguish between fasting, pre-prandial, and post-prandial hyperglycaemia; quantify glycaemic excursions; identify or confirm hypoglycaemic episodes; and provide immediate feedback to patients about the impact of food choices, physical activity and antidiabetic medication on their glycaemic control.

We have analysed SMCG profiles in 592 patients with inadequate glycaemic control on dual oral therapy in 58 UK clinical centres, observed over five visits from randomisation to one year, randomised to three different insulin regimens in the Treating To Target in Type 2 Diabetes (4-T) trial[1]. Each SMCG profile consisted of eight finger-prick glucose measurements taken pre-breakfast, 2 hours after breakfast, pre-lunch, 2 hours after lunch, pre-dinner, 2 hours after dinner, pre-bed and 3 AM. The number of SMCG profiles available for patients randomised to the addition of Biphasic, Prandial or Basal analogue insulin with both baseline and one-year data were 195, 196, 201 respectively. Mean (SD) HbA1c values for the three groups at baseline were 8.6 (0.8), 8.6 (0.8) & 8.4 (0.8) with mean (SD) changes between baseline and 1 year fasting, post-prandial and 3 AM glucose values of 45 mg/dl (56), 68 mg/dl (63) and 52 mg/dl (70); fasting and postprandial glucose levels being significantly different among treatments ($p < 0.001$)[1].

Statistical analysis of such time-dependent clinical measures is not straightforward, especially when the glycaemic variations for a particular patient are highly sensitive to instantaneous physiological & clinical changes. The normal practice of reporting such data with overall means of the profiles compared between treatments is misleading, as this approach ignores the inherent heterogeneity and the volatility of glycaemic profiles. However, it is very important to appropriately capture both the within-day and day-to-day variability in glucose measures to predict with sufficient precision the likelihood of imminent hypoglycaemia or hyperglycaemia in order that a proactive glycaemic management tool can be developed. We propose multilevel mixed models incorporating a random component to account for multicentre effects, which compares the efficacy of three treatment regimens, separately for the pre and post prandial glycaemic scenarios. Within-day day specific models have been developed to assist a more effective “insulin dose titration” algorithm for future studies. The day-to-day longitudinal aspects of the data are well taken care of, with exploration of various correlation structures. The glycaemic variations were explored having adjusted for the effects of relevant clinical and demographic factors.

[1] Holman et al. (2007): Addition of Biphasic, Prandial, or Basal Insulin to Oral Therapy in Type 2 Diabetes. *NEJM 357 (17)*: 1716-1730.