Unravelling the Dynamics of Insulin Dose and Changes in Weight and HbA1c

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Insulin therapy decreases HbA1c in diabetic patients but often leads to increased weight. We sought to unravel this three-way relationship by developing a methodology to estimate the net effect of weight on HbA1c, after eliminating effects of insulin on HbA1c and weight.

We used data from the Treating-To-Target-in-Type 2 diabetes trial which randomized 708 insulin-naive patients to 12-month's basal, biphasic or prandial analog insulin therapy. Patients were mean($\pm$ISD) age 62$\pm$9 years, HbA1c 8.5$\pm$0.8%, weight 86$\pm$16kg and median(IQR) 9 (6,13) years diabetes duration. Insulin dose, weight and HbA1c were recorded three-monthly.

To estimate hypothetical insulin-eliminated values for HbA1c (H*) and weight (W*), we developed Residual Regression and Local Smoothing Regression approaches to take into account likely multiplicative and inconsistent effects of insulin. At 12 months, H* was 0.22% higher and W* 0.8kg lower than their observed values. These differences varied between biphasic, basal and prandial insulin groups, being +0.25, -0.07 and +0.43% for H* and -4.1, -0.3 and -1.6kg for W* respectively.

Errors-in-Variables regression models were developed to estimate W* impact on H*, and assuming H* and W* are measured with 90% reliability. Analyses by quartiles of baseline HbA1c suggest that at twelve months a 3kg W* increment would be associated with a 0.2% rise in H*. This rise would be 0.4% for those with a baseline HbA1c >9%, compared with those <8%.

This novel methodology can assist with the interpretation of the time-varying inter-relationships and dynamics of important clinical parameters in people with type 2 diabetes. It should help predict the glycaemic control achievable with different treatment regimens in clinical trials and better inform glycaemic management in clinical practice. Such techniques could also help to determine optimum insulin doses.[table1]

Month	Insulin Dose (IU/day)	Observed Weight (Kg)	W* (Kg)	Observed HbA1c (%)	H* (%)	Effect of W* on H*
3	32	88.6	87.0	7.3	7.51	0.02 (p < 0.001)
6	38	88.9	88.1	7.20	7.51	0.02 (p < 0.001)
9	42	88.6	88.3	7.20	7.48	0.03 (p < 0.001)
12	48	89.4	88.6	7.20	7.42	0.16 (p < 0.001)