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Background

Achieving adequate hypoglycaemia during the insulin tolerance test (ITT) is important given that this is crucial for evaluation of the growth hormone (GH) and cortisol secretion. Excessive hypoglycaemia is undesirable given that it is has been reported to be associated with mortality. We aim to evaluate factor affecting insulin sensitivity and hypoglycaemia during ITT.

Objectives

- 1) To describe dynamic changes in glucose during ITT from mathematical simulation.
- 2) To evaluate factors affecting depth and timing of hypoglycaemia during ITT using formal plasma glucose and also mathematical simulated glucose.

Methods

Retrospective study of 106 children (76M) who had an ITT (Actrapid 0.1units/kg) performed between 2009-2013 for evaluation of short stature, poor growth or re-assessment after completion of growth following rhGH therapy. Plasma glucose, cortisol and GH were measured at -30, 0, 15, 30, 60, 90, 120 minutes following administration of IV insulin. Mathematical modelling using second order negative feedback was used to study dynamic changes in glucose (simulated glucose) taking into account production and clearance rates. The slope of the change in glucose clearance rate versus its concentration was defined as insulin sensitivity. Adequate hypoglycaemia was defined as glucose < 2.2mmol/L. Results reported as median (range).

Results continued

Fig 2: Simulated glucose using negative feedback model following insulin administration

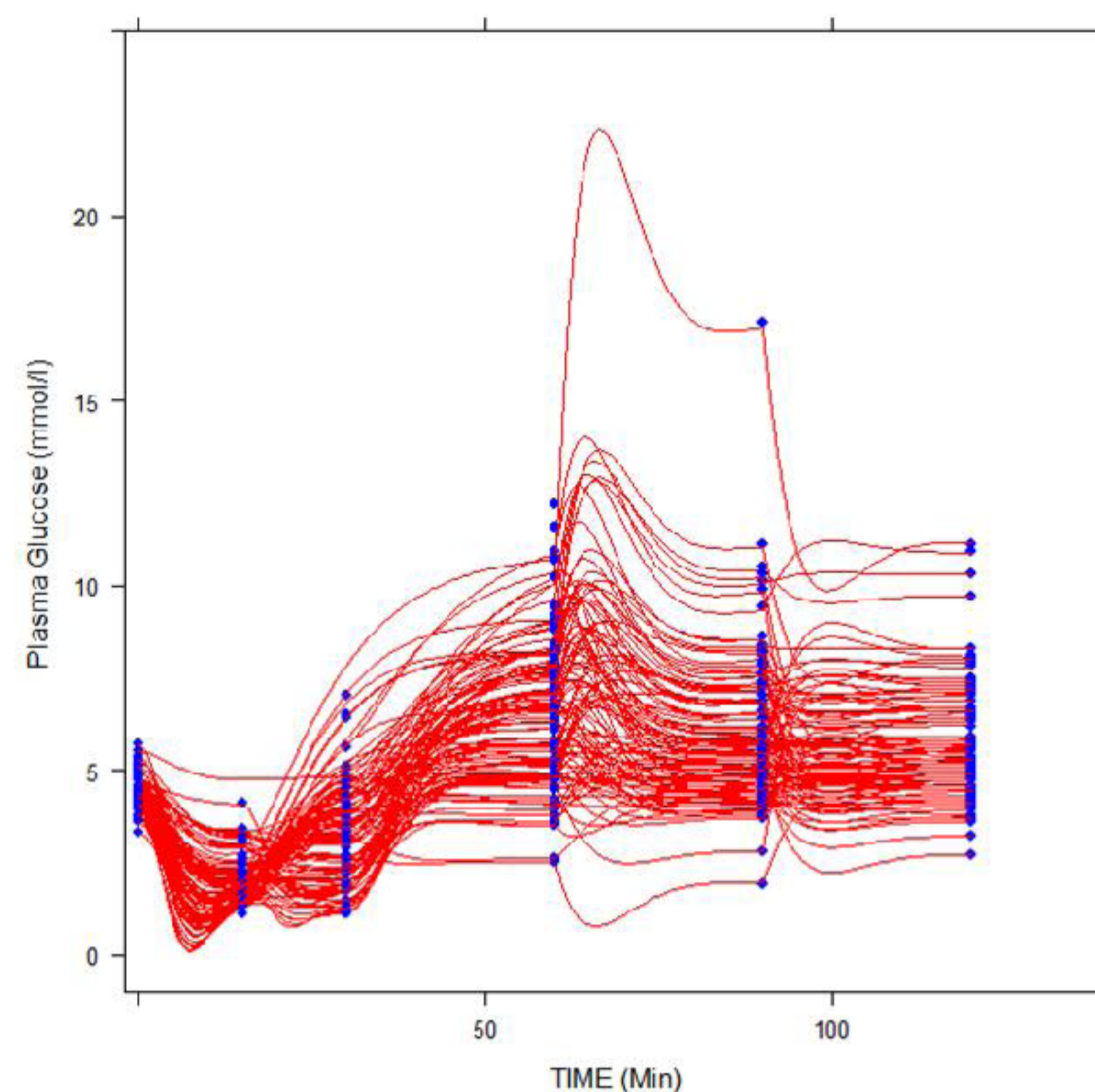


Fig 3: Simulated change in glucose from baseline using negative feedback model following insulin administration

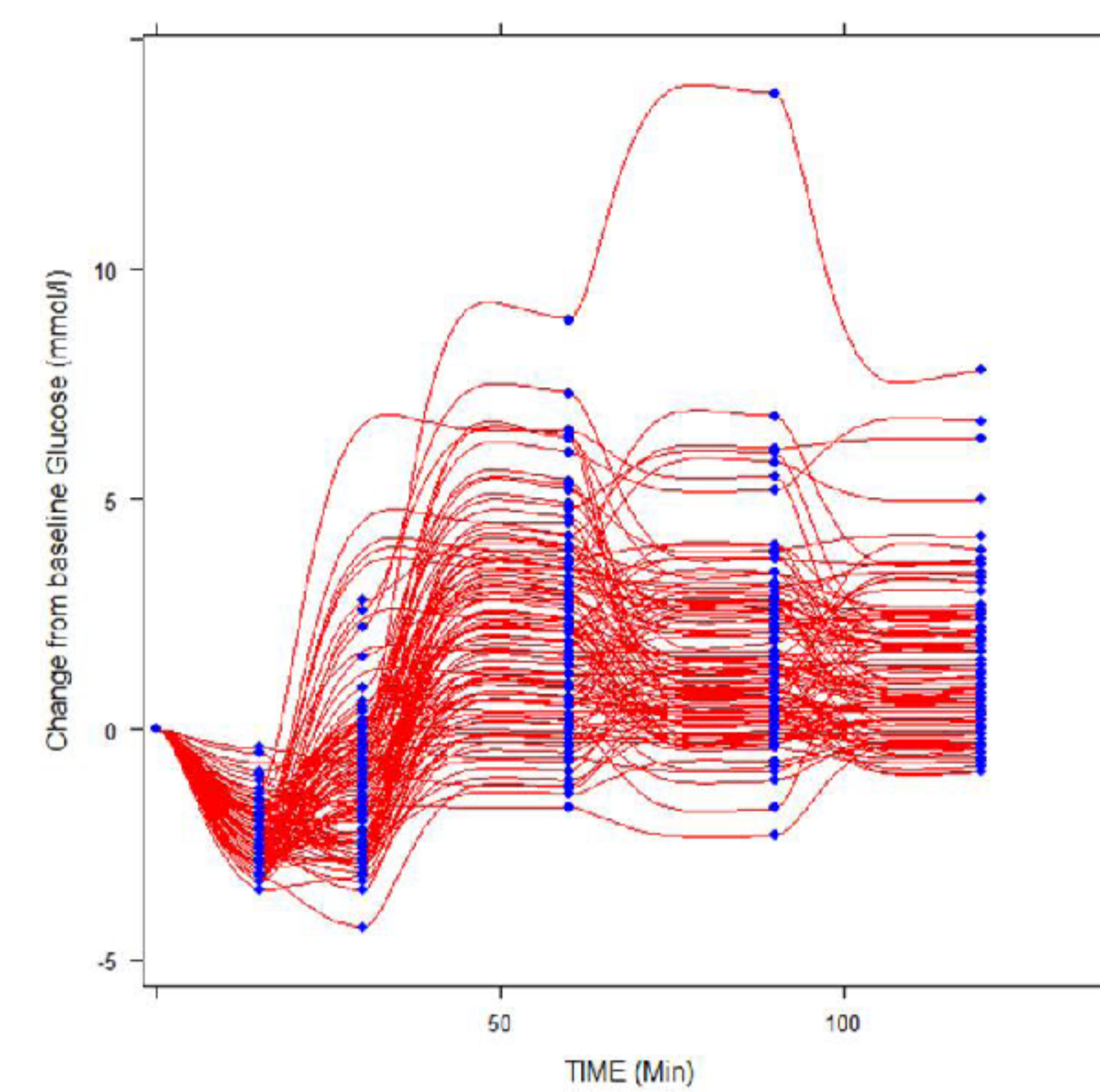
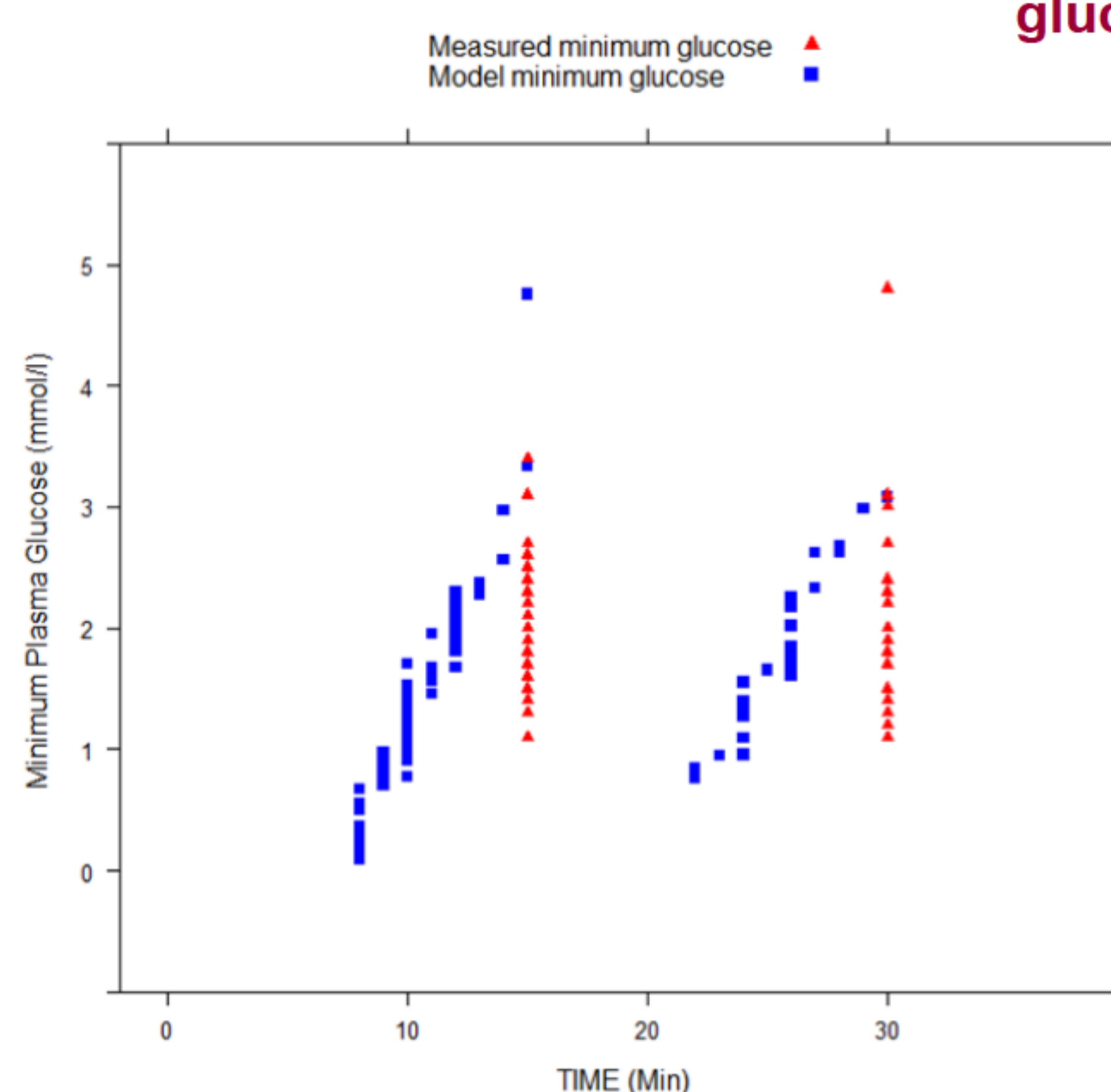


Fig 4. Timing of minimum glucose (measured plasma glucose and simulated glucose)



Nadir for measured plasma glucose occurred at **15min (15,30)**.

Nadir for simulated glucose occurred at **11min (8, 29)**.

Of the 22 who did not achieve adequate hypoglycaemia based on measured plasma glucose, **8(36.4%)** achieved adequate simulated hypoglycaemia at 13.5min(11,29).

In a multivariate model, there was a trend for children with GH deficiency to have greater insulin sensitivity (95%CI 0.0, 0.60).

In multivariate analysis (age, gender, puberty, body surface area, baseline glucose), baseline glucose was the only significant independent factor associated with the extent (p=0.009, 95%CI=0.14,0.93) and timing of simulated nadir glucose (p=0.005, 95%CI=1.58,8.79)

Conclusion

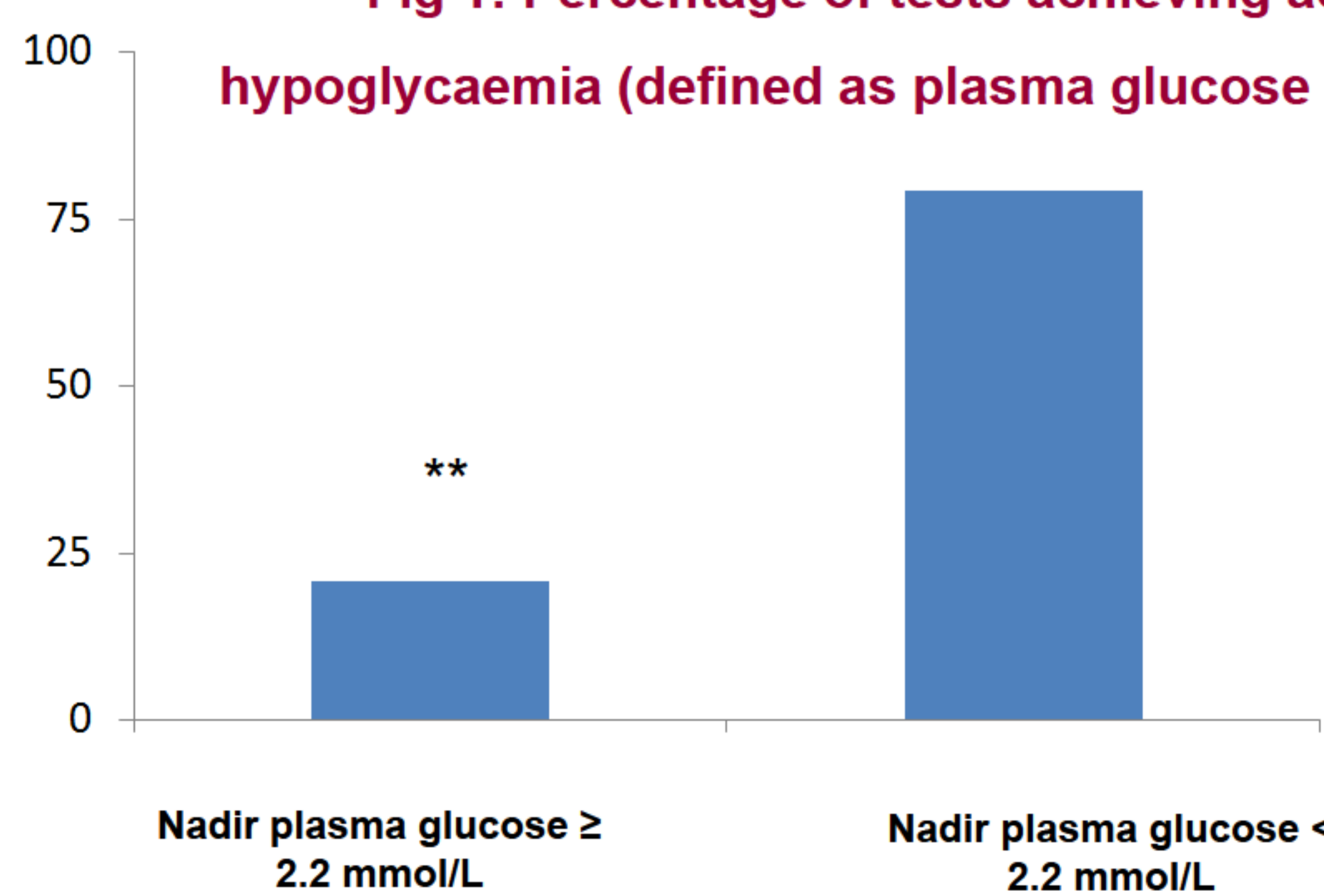
- 1- 20% of children who underwent ITT were classified as achieving inadequate hypoglycaemia based on plasma glucose.
- 2- However, based on the simulation model, over one third of these children would have achieved adequate hypoglycaemia.
- 3- Given that the identification of GH and cortisol deficiency on ITT critically depends on optimal hypoglycaemia, these results have important clinical implications.
- 4- Baseline blood glucose was the only significant predictive factor of timing and depth of hypoglycaemia in our study, although larger studies should evaluate the impact of clinical diagnosis on this.

Results

Median age of the group was 12.7 years (5.7,19.3), Ht SDS-2.8 (-4.2,1.5), BMI SDS-0.1(-4.0, 4.4).

Percentage

Fig 1: Percentage of tests achieving adequate hypoglycaemia (defined as plasma glucose < 2.2 mmol/L)



Simulation showing transition between two measurements using the negative feedback mathematical model

The negative feedback mathematical model

