Glucocorticoids, Insulin Sensitivity & Tight Glycemic Control in the ICU

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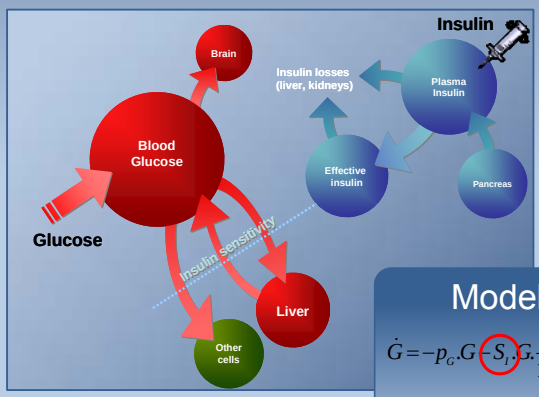
Background

- Glucocorticoids reduce insulin sensitivity in healthy individuals by 30-62%.
- They are used in critical care to treat a variety of inflammatory and allergic disorders, but may inadvertently exacerbate stress-hyperglycemia through reduced insulin sensitivity.
- This research uses model-based methods to determine the extent to which glucocorticoids reduce insulin sensitivity in critically ill patients and how it affects tight glycaemic control (TGC).



Model equations

$$\dot{G} = -p_G.G - S_I.G.\frac{Q}{1+\alpha_G Q} + \frac{P(t)+EGP-CNS}{V_G(t)}$$

$$\dot{I} = -\frac{nI}{1+\alpha_I I} + \frac{u_{ex}(t)}{V_I} + e^{-(k_I u_{ex}(t))} I_B$$

$$\dot{Q} = -kQ + kI$$

Glucose Absorption

$$P(t) = \min(d_2 P_2, P_{max})$$

$$\dot{P}_2 = -\min(d_2 P_2, P_{max}) + d_1 P_1$$

$$\dot{P}_1 = -d_1 P_1 + D(t)$$

Table 1. Cohort statistics

	Control Cohort	Steroid Cohort	
N	40	40	
Mortality (%)	20	25	p = 0.39[a]
Operative/Non-operative	13/27	12/28	p = 0.68[a]
AGE (yrs)	63.5 [45-73]	59.5 [49-73]	p = 0.89[b]
APACHE II Score	19 [16-27]	21.5 [18-26]	p = 0.53[b]
APACHE II Risk of death (%)	33.6 [22-53]	33.9 [21-59]	p = 0.72[b]
Patient time on SPRINT (hrs)	129.5 [64-189]	116.5 [90-186]	p = 0.53[b]
Patient median blood glucose (mmol/l)	5.8 [5.4-6.2]	6.0 [5.8-6.4]	p = 0.08[b]
Equivalent daily dose of hydrocortisone (mg)	0	160 [80-200]	
Total time on Steroids (hrs)	0	4625	
Total time on SPRINT (hrs)	7149	5844	

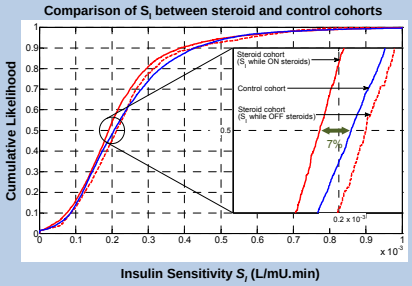


Figure 1. Cohort analysis

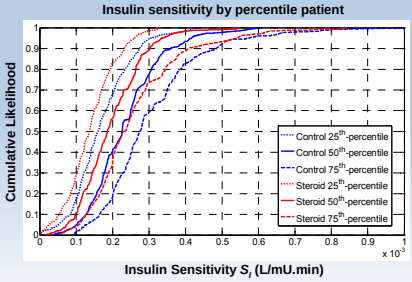


Figure 2. Percentile-patient analysis

Subjects & Methods

- A retrospective study using data from 80 patients admitted to the Christchurch Hospital Intensive Care Unit (ICU) between 2005 and 2007.
- Two cohorts of 40 patients matched for overall cohort statistics (Table 1). Patients in one group received glucocorticoid treatment, while patients in the other group received none.
- Patients were excluded if they received β-blocker treatment as it can affect glucose metabolism.
- All patients were on the SPRINT TGC protocol for 24+ hours.
- A clinically validated glucose-insulin system model was used to identify an insulin sensitivity (S_I) parameter every hour for every patient.
- The model-based insulin sensitivity was used to quantify differences between the cohorts.
- *In-silico* virtual trial simulations were performed to determine the clinical impact of these differences on TGC

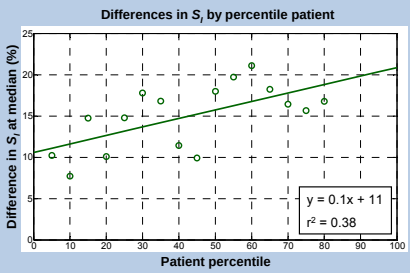
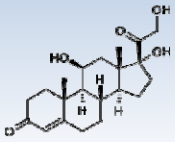


Figure 3. Differences in S_I across percentile patients



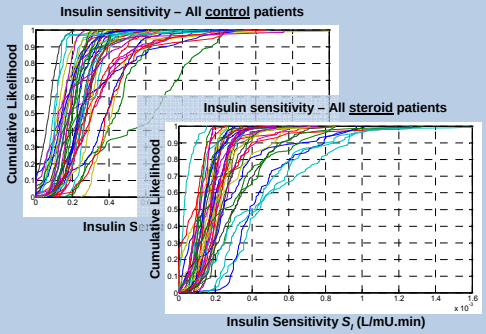


Figure 4. Individual patient insulin sensitivity CDF plots

Results

- A 7% reduction in insulin sensitivity was seen for patients receiving glucocorticoids compared to the control group (Figure 1).
- Per-patient analyses showed 8-21% reductions in insulin sensitivity at the median (Figures 2 & 3) for patients in the steroid group.
- Higher percentile-patients tended to show greater suppression of S_I with administration of steroids (Figure 3).
- Virtual trial simulations indicate that there is **no clinically significant difference in glycemic control** achieved under the SPRINT protocol with changes in S_I of 10-20%.

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