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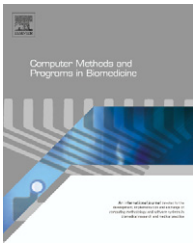

Impact of glucocorticoids on insulin resistance in the critically ill

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ABSTRACT

Glucocorticoids (GCs) have been shown to reduce insulin sensitivity in healthy individuals. Widely used in critical care to treat a variety of inflammatory and allergic disorders, they may inadvertently exacerbate stress-hyperglycaemia. This research uses model-based methods to quantify the reduction in insulin sensitivity from GCs in critically ill patients, and thus their impact on glycaemic control. A model-based measure of insulin sensitivity (S_I) was used to quantify changes between two matched cohorts of 40 intensive care unit (ICU) patients. Patients in one cohort received GC treatment, while patients in the control cohort did not. All patients were admitted to the Christchurch hospital ICU between 2005 and 2007 and spent at least 24 h on the SPRINT glycaemic control protocol.

A 31% reduction in whole-cohort median insulin sensitivity was seen between the control cohort and patients receiving glucocorticoids with a median dose equivalent to 200 mg/d of hydrocortisone per patient. Comparing percentile patients as a surrogate for matched patients, reductions in median insulin sensitivity of 20%, 25%, and 21% were observed for the 25th-, 50th- and 75th-percentile patients, respectively. These cohort and percentile patient reductions are less than or equivalent to the 30–62% reductions reported in healthy subjects especially when considering the fact that the GC doses in this study are 1.3–4.0 times larger than those in studies of healthy subjects. This reduced suppression of insulin sensitivity in critically ill patients could be a result of saturation due to already increased levels of catecholamines and cortisol common in critically illness. Virtual trial simulation showed that reductions in insulin sensitivity of 20–30% associated with glucocorticoid treatment in the ICU have limited impact on glycaemic control levels within the context of the SPRINT protocol.

1. Introduction

Hyperglycaemia is prevalent in critical care [1–5]. Increased secretion of counter-regulatory hormones stimulates endogenous glucose production and reduces effective insulin sensitivity [3,4,6]. Studies by Van den Berghe et al. [5,7], Krinsley [8] and Chase et al. [2] have shown that tight glucose control can reduce ICU mortality by 18–45%. Glucocorticoids are used in critical care to treat a variety of inflammatory and allergic disorders, but may exacerbate stress-hyperglycaemia through

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their side effect of reducing insulin sensitivity and may thus indirectly impact clinical outcome.

Studies have shown that glucocorticoids (GCs) increase insulin resistance (reduce insulin sensitivity) in healthy individuals [9–13]. However, there is a lack of data about whether this effect is equally valid, or equally large, for critically ill patients. Insulin resistance, defined by relatively low insulin-mediated glucose disposal, is common and can be extreme in critically ill patients, which makes tight glycaemic control (TGC) in intensive care unit (ICU) patients difficult. Treatment with GCs may therefore make this task even harder if they yield significant (further) reductions of insulin sensitivity. Model-based methods can readily quantify changes in the insulin resistance of critically ill patients where typical methods of assessing this metric may be difficult to apply.

Several studies have reported 30–62% decreases in insulin sensitivity of healthy subjects after short-term administration of dexamethasone (2 or 6 mg/d) [9–12]. Pagano et al. [13] documented a similar change with prednisone (15 mg/d). The mechanisms and pathways underlying these dramatic reductions in insulin sensitivity are not yet fully understood. Metabolic adaptations, including enhanced endogenous glucose production (EGP), increased plasma insulin concentrations, and reduced whole-body glucose disposal were also reported in these studies.

The primary hypothesis of this research is that insulin sensitivity is reduced by glucocorticoids in critically ill patients, but potentially to a lesser extent than in healthy individuals. Therefore, the aim of this research is to use model-based methods to quantify the effect of glucocorticoid therapy on insulin sensitivity of ICU patients and its impact on the resulting TGC interventions. These results will, for matched cohorts, enable assessment of whether GC therapy in the critically ill is detrimental to achieving tight glycaemic control, and thus potentially to patient outcome.

2. Materials and methods

2.1. Subjects

This research was conducted as a retrospective study using records from 80 patients admitted to the Christchurch ICU between 2005 and 2007. A model-based measure of insulin sensitivity (S_I) was used to quantify changes between two matched, critically ill cohorts.

A cohort of 40 patients, who each spent 24 h or more on the SPRINT glycaemic control protocol [2] and received glucocorticoid therapy during this time, was selected from the available records. These patients had received treatment with one or more of the steroids listed in Table 1. The per-patient median steroid dose was equivalent to 200 mg/d of hydrocortisone [14–16]. Patients were excluded if they received β-blockers or ACE-inhibitors, as these therapeutics can affect glucose metabolism and insulin sensitivity in an opposing fashion [17–19].

In cases where patients did not receive steroid therapy for the entire time they were on SPRINT, insulin sensitivity was considered to be affected by the drug for one effective biological half-life following the last dose. This period ensured that any effects of the exogenous glucocorticoids on insulin sensitivity had not reduced so far as to be undetectable or swamped by elevated levels of circulating endogenous cortisol, which is also common in critically ill patients [20]. However, this short period precludes useful comparison between on- and off-steroid insulin sensitivities within the cohort as exogenous glucocorticoids may have a significant effect on S_I in some patients for longer than one half-life.

Table 1 – Glucocorticoids and their properties used in this study [14–16].

Compound	Relative anti-inflammatory potency	Duration of action/effective biological half-life (h)
Hydrocortisone	1	10
Prednisone	4	24
Prednisolone	4	24
Methyl-prednisolone	5	24
Dexamethasone	25	45

Relative potencies and biological half-lives of the glucocorticoids were based on data for anti-inflammatory effects as these closely parallel the effects on glucose metabolism [16]. Table 1 lists the potencies and half-lives used in analysis of the steroids for this research.

A control cohort of 40 patients, who did not receive any glucocorticoid, β-blocker or ACE-inhibitor therapy, was also selected from patients on the SPRINT protocol. Patients were selected so that the overall cohort parameters (age, sex, outcome, severity of illness), shown in Table 2, matched the steroid cohort as closely as possible. While the cohorts are matched for overall glycaemic levels, the control cohort had more time in the 4.0–7.0 mmol/L glycaemia band than the steroid cohort.

The SPRINT protocol is a simple, lookup-table system derived from a model-based controller that modulates insulin and nutritional inputs. The protocol titrates insulin doses and nutrition rates to patient-specific insulin sensitivity for tight glycaemic control [2,21,22]. SPRINT has been used in the Christchurch ICU since August 2005 on more than 1000 patients. The requirement for patients in this study to be on the SPRINT protocol ensures they have regular, consistent and accurate records of blood glucose level, and insulin and nutrition administration. It also ensures the two cohorts have clinically very similar levels of glycaemic control, as this study focuses on the potential impact of glucocorticoids on TGC. The use of these patient records falls under existing ethics approval granted by the Upper South Regional Ethics Committee, New Zealand.

2.2. Model-based insulin sensitivity

This study used a model based on the clinically validated glucose–insulin models of Le Compte et al. [23] and Lotz et al. [24]. The model-based insulin sensitivity has been shown to correlate well with the insulin sensitivity index (ISI) determined by the gold-standard hyperinsulinaemic–euglycaemic clamp ($r > 0.90$) [24]. Implementing this model in Matlab™ (Mathworks, Natick MA) with ICU patient data, an S_I value was identified every hour for every patient while on the SPRINT