Hypoglycemia Increases Serum Interleukin-6 Levels in Healthy Men and Women
(Hypoglycemia and IL-6)

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**ABSTRACT**

*Objective:* Inflammation may have a major role in the pathogenesis and prognosis of critical illness. Hyperglycemia increases levels of the inflammatory cytokine interleukin-6 (IL-6) and is associated with increased risks of morbidity and mortality. Since hypoglycemia is also associated with adverse outcomes, we tested the hypothesis that hypoglycemia increases IL-6.

*Research Design and Methods:* Seventeen healthy men and women participated in hypoglycemic and euglycemic hyperinsulinemic clamp studies (target blood glucose 2.7 and 5.0 mmol/l, respectively), separated in time by 1-3 months. IL-6, ACTH, and cortisol were measured at baseline and 45, 75, 105 and 135 minutes after initiation of the insulin infusion.

*Results:* IL-6, ACTH, and cortisol increased significantly (p<0.0001) during hypoglycemia but not euglycemia. IL-6 increased from 1.0 ± 0.2 pg/ml at baseline to 2.6 ± 0.2 pg/ml after 135 minutes of hypoglycemia, whereas IL-6 levels were unchanged during euglycemia.

*Conclusions:* Hypoglycemia increases IL-6 levels in healthy individuals.
Hyperglycemia and hypoglycemia are associated with increased risks of morbidity and mortality in critically ill patients (1,2). In intensive care unit (ICU) patients, hyperglycemia is associated with elevated levels of interleukin-6 (IL-6), an inflammatory cytokine that may have a role in the pathogenesis and prognosis of critical illness (1). Acute hyperglycemia increases IL-6 levels in healthy individuals (3). The goal of this study was to determine if hypoglycemia stimulates IL-6 levels.

RESEARCH DESIGN AND METHODS
Euglycemic and hypoglycemic hyperinsulinemic clamp studies were performed, in random order, separated in time by 1-3 months, in healthy volunteers, who were not taking any medications. The Institutional Review Boards approved study protocols. Informed consent was obtained. For five days before each study, subjects consumed an 125 ± 10 mEq/day sodium, 100 ± 10 mEq/day potassium and 800 ± 50 mg/day calcium isocaloric diet. Subjects were admitted to the General Clinical Research Center and were asked to fast and remain supine after midnight. Clamp studies were performed in the morning with insulin (80 mU/m² body surface area/minute, Novolin R, Novo Nordisk, Princeton, NJ) infused for 135 minutes. Dextrose (20%) was infused to maintain glucose levels at 5.0 and 2.7 mmol/l for euglycemic and hypoglycemic clamps, respectively. In one subject the insulin infusion rate was increased by 50% at T=77 min to achieve target hypoglycemia. Serum glucose levels during the insulin infusions were similar for hypoglycemic and euglycemic studies, 723.4 ± 16.7 and 729.2 ± 42.4 pmol/l, respectively. Serum glucose levels decreased to 2.79 ± 0.05 mmol/l by 30 minutes and averaged 2.79 ± 0.02 mmol/l for the remainder of the hypoglycemic clamp (Figure 1A). Glucose levels were 4.91 ± 0.03 mmol/l during the euglycemic clamp.

During hypoglycemic and euglycemic studies, baseline measurements were similar for IL-6 (1.0 ± 0.2 versus 1.5 ± 0.3 pg/ml), ACTH (7.4 ± 0.6 versus 7.6 ± 0.6 pmol/l) and cortisol (291 ± 25 versus 268 ± 13 nmol/l). There were significant (p<0.001) increases in IL-6, as and anticipated in ACTH and cortisol, during hypoglycemia as compared with euglycemia (Figure 1). IL-6 levels increased from 1.0 ± 0.2 pg/ml at

Serum was analyzed for IL-6 (R&D Systems, Inc., Minneapolis, MN), cortisol (Access Cortisol Immunoassay, Beckman Coulter, Chaska, MN) and insulin (Access High Sensitive Insulin Immunoassay, Beckman Coulter). Plasma was assayed for ACTH (DiaSorin ACTH IRMA, DiaSorin, Stillwater, MN). Data was analyzed using repeated measures analysis of variance with main effects of treatment (hypoglycemia and euglycemia) and time (baseline, 45, 75, 105, and 135 min). Non-repeated measures were analyzed using Student’s two-tailed t test. Data are expressed as mean ± standard error of the mean.

RESULTS
We studied nine women and eight men (age 28.9 ± 2.0 years, BMI 23.5 ± 0.7 kg/m², systolic blood pressure 106.6 ± 2.4 mmHg, diastolic blood pressure 68.5 ± 2.1 mmHg). Baseline glucose, insulin, and HOMA index did not differ between euglycemic and hypoglycemic studies, averaging 5.08 ± 0.06 mmol/l (glucose), 24.0 ± 2.4 pmol/l (insulin), and 1.32 ± 0.38 (HOMA index). There were significant (p<0.001) increases in IL-6, and as anticipated in ACTH and cortisol, during hypoglycemia as compared with euglycemia (Figure 1). IL-6 levels increased from 1.0 ± 0.2 pg/ml at
baseline to 2.6 ± 0.2 pg/ml at the end of the hypoglycemic study. There was no significant change in IL-6 during the euglycemic clamp, 1.5 ± 0.3 pg/ml at baseline versus 1.6 ± 0.3 pg/ml at end of the study. The increase in IL-6 with hypoglycemia did not correlate with BMI, HOMA index, or increases in ACTH or cortisol.

CONCLUSIONS

Serum IL-6 levels increase in response to prolonged (> 60 min) insulin-induced hypoglycemia. This increase is similar in magnitude to the IL-6 increase induced by hyperglycemia and endotoxin in healthy individuals (3,4). While our results differ from a small study, showing no effect of hypoglycemia on IL-6 (5), this difference is likely due to the longer duration of hypoglycemia in the current study.

IL-6 has multiple physiological actions that affect glucose metabolism and may underlie the association of IL-6 with the development of insulin resistance and type 1 and 2 diabetes (6). Although the current study design does not allow us to determine cause and effect relationships between IL-6 and ACTH or cortisol during hypoglycemia, IL-6 is known to stimulate all levels of the hypothalamic-pituitary-adrenal axis. In humans, IL-6 administration increases cortisol, glucagon and blood glucose levels (7). Thus, IL-6 may aid in the counterregulatory response to hypoglycemia, especially during prolonged hypoglycemia.

IL-6 influences inflammation and immune function (6). IL-6 levels are also elevated in hyperglycemic ICU patients and acute hyperglycemia increases IL-6 in healthy subjects (1,3,4). Our finding that IL-6 levels increase with hypoglycemia in healthy subjects raise the possibility that IL-6 levels will be elevated in hypoglycemic ICU patients. This possibility is relevant given the recent emphasis on achieving euglycemia in ICU patients through intensive intravenous insulin administration, which increases the risk of severe hypoglycemia (2). Interestingly, recent insulin infusion trials in medical ICU patients fail to show clear benefits with tight glycemic control (2).

Our finding coupled with those in the literature lead us to conclude that both hypoglycemia and hyperglycemia increase IL-6 levels. Additional studies are needed to determine whether hypoglycemia-induced increases in IL-6 affect health outcomes in acutely ill patients.

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FIGURE LEGEND

FIGURE 1. Serum glucose levels (A) and change in serum IL-6 (B), plasma ACTH (C) and serum cortisol (D) from baseline levels during euglycemic hyperinsulinemic clamps (dark squares) and hypoglycemic hyperinsulinemic clamps (open circles). Horizontal lines in panel A indicate the target glucose levels of 5.0 mmol/l for euglycemia and 2.7 mmol/l for hypoglycemia. Data are mean +/- standard error of the mean.