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Intensive blood glucose control in acute and prolonged critical illness: endogenous secretion contributes more to plasma insulin than exogenous insulin infusion

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Abstract

We investigated the contribution of impaired insulin secretion (observed as dynamics of C-peptide) and insulin resistance (measured by euglycemic clamps) to glucose dysregulation in 20 critically ill patients after severe trauma during feeding and intensive glucose control with intravenous insulin. Between the fourth and seventh day when insulin sensitivity is lowest, insulin secretion is highest and supranormal despite tight control of blood glucose by exogenous insulin. Afterward, plasma C-peptide decreases together with an improvement in insulin sensitivity. Multiple regression analysis revealed that plasma insulin is determined more by endogenous secretion than insulin infusion, even during the acute phase when exogenous insulin requirements are high.

1. Introduction

Hyperglycemia in critically ill nondiabetic patients is very common [1], and most intensive care unit (ICU) patients probably benefit from tight glucose control by continuous intravenous (IV) insulin infusion [2,3]. Thus, most ICU patients are treated with continuous IV insulin infusion. We asked to what extent this treatment influenced plasma insulin concentration in comparison with endogenous insulin secretion. We also attempted to describe the changes of insulin resistance during the transition from an acute to prolonged phase of critical illness.

2. Methods

We conducted a prospective study on multiple trauma patients (n = 20; male = 17; female = 3; age, 40 ± 16 years; body mass index, 27 ± 4 kg m^{-2}; Injury Severity Scale = 39 ± 14; Acute Physiology and Chronic Health Evaluation II score, 24 ± 8) who were expected to require ventilator support for at least 2 weeks, mainly because of severe head injury or chest trauma. We excluded patients expected to die or having diabetes. The Ethics Committee approved the protocol, and the closest relatives of the subjects gave their informed consent. During the study, 2 patients received hydrocortisone in substitution doses (up to 150 mg/d) for a period up to 5 days. Only norepinephrine was used as a vasopressor: the number of treated patients declined from 15 (75%) at day 4 (average dose, 0.07 ± 0.05 μg kg^{-1} min^{-1}) to 1 (5%) at day 17. No other drugs with a known influence on insulin secretion or sensitivity were given to study subjects, excluding β-blockers. The study subjects were fed preferably by the enteral route (Diason Low Energy; Nutricia, Prague, Czech Republic) and supplemented with parenteral nutrition to reach a nutritional goal of 1.5 g amino acids per kilogram per day and 80% of energy expenditure measured daily by indirect calorimetry. The proportion of calories provided enterally increased from ~30% at the beginning of the study to ~60% in the end. Blood glucose was measured in at least 3-hour intervals and corrected with IV insulin (Actrapid; Novo Nordisk, Copenhagen, Denmark) according to a nurse-directed protocol [4]. Plasma insulin

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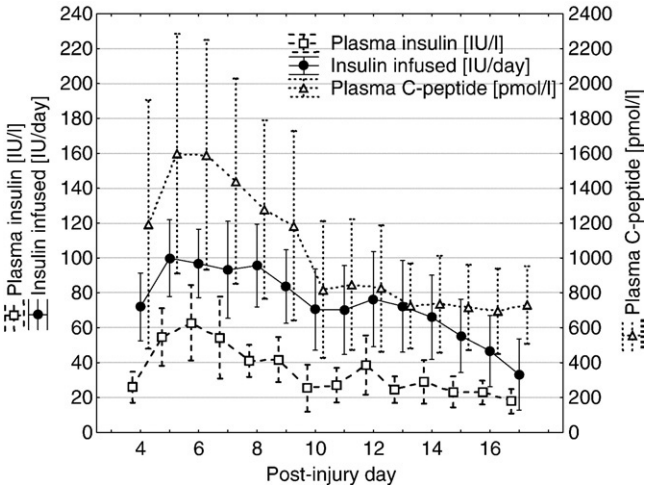

Fig. 1. Plasma insulin and exogenous insulin dose (left x-axis) and plasma C-peptide (right y-axis) after multiple trauma. Vertical bars designate 95% confidence intervals.

and C-peptide concentrations were assessed (Immulite 2000; Diamond Diagnostics, Holliston, MA) daily at 5 AM until day 17. At days 4, 10, and 17, nutrition was interrupted at 2 AM; and between 8 AM and 10 AM, euglycemic hyperinsulinemic clamp [5] (insulin dose, 60 mIU m^{-2} min^{-1}, leading to insulinemia, 69 ± 23 IU/L) was performed to assess insulin resistance.

3. Results

Two patients died during the study, and 1 was discharged from the ICU. Seventeen patients finished the study. All available data are included in the analysis. Glucose intake was constant during the study (192 ± 57 g/d; influence of time, $P = .33$; analysis of variance) as well as the blood glucose concentration (6.21 ± 1.41 mmol/L, $P = .14$; of 1986 recorded values, 51% were within target, 4.5-6.1 mmol/L). All patients required exogenous insulin to achieve glycemic control. Insulin concentrations declined through the study ($P < .001$) because of a decrease in both insulin secretion (plasma C-peptide, $P = .007$) and exogenous insulin dose ($P < .001$) (Fig. 1). Glucose disposal rates during clamps adjusted to body surface area; and plasma insulin were 9.9 ± 2.4, 18.3 ± 2.2, and 18.2 ± 2.1 μmol L IU^{-1} min^{-1} m^{-2} at days 4, 10, and 17 ($P = .036$). To assess to what extent the plasma insulin concentration was dependent on exogenous infusion, we created a multiple regression model [6] with plasma insulin as the dependent variable and exogenous insulin dose and plasma C-peptide as independent variables and observed β-coefficients and their significance to both dependent values each study day. In our regression model, we set the intercept to zero assuming zero plasma insulin in the absence of exogenous infusion and endogenous secretion. The β-coefficients are the coefficients we would have obtained had we first standardized all of our variables to a mean of 0 and a standard deviation of 1. Thus, the magnitude of these β-coefficients allows us to compare the relative contribution of both independent variables in the prediction of the dependent variable. During the study, plasma insulin depended more on endogenous secretion (β from .65 to .85, P from <.0001 to .006) and less on exogenous delivery (β from .12 to .35, P from .002 to .087). This applied for any study day; and no trend to change was apparent, although the overall model remained highly significant (P always <.0001).

4. Discussion

Our results demonstrate that insulin sensitivity improves between the 0 and 14 days after multiple trauma and then remains stable. Despite high doses of exogenous insulin that are necessary to control blood glucose, endogenous insulin secretion remains the main source of plasma insulin during both acute and protracted critical illness. We started our study at day 4 after injury, when volume resuscitation was completed; and the subjects were given only very low doses of catecholamines, which do not influence insulin secretion [7]. During the first week, there was the highest degree of insulin resistance; and highest doses of exogenous insulin had to be infused to achieve blood glucose control. At the same time, endogenous insulin secretion peaked as well. Afterward, the plasma insulin concentration required to dispose of the constant glucose load continually decreased. Endogenous insulin secretion was shown to be an important factor contributing to plasma insulin, even during the acute phase of a critical illness when most patients are dependent on high doses of exogenous insulin and older reports suggested the presence of an absolute insulin deficiency [8]. In conclusion, during both acute and protracted phases of critical illness, plasma insulin is determined more by endogenous secretion than by the infusion of exogenous insulin, which is used to control blood glucose during artificial nutrition.

Acknowledgment

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