

Nonlinear Metabolic Effect of Insulin across the Blood Glucose Range in Patients with Type 1 Diabetes Mellitus

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Abstract

Background:

For insulin therapy to successfully maintain blood glucose (BG) levels of patients with type 1 diabetes mellitus (T1DM) in normoglycemia, it is necessary to understand if the metabolic effect of insulin across the BG range is linear or not.

Methods:

We assess the ability of insulin to lower BG in patients with T1DM in hypoglycemia and hyperglycemia. The net metabolic effect of insulin, defined as the total effect resulting from both reduced endogenous glucose production and increased glucose uptake, was used to define the insulin effectiveness (IE), a measure that indicates the amplitude of glucose lowering that a unit of active insulin can achieve at a given BG level. The IE was assessed in hypoglycemia and hyperglycemia through two separate studies. In the first study, patients were subjected to a hyperinsulinemic euglycemic and hypoglycemic glucose clamp. In the second study, another group of patients were clamped at a hyperglycemic level.

Results:

The IE increased by 75% when BG dropped from 90 to 50 mg/dl at a steady rate of 1 mg/dl/min and decreased by 10% when BG was increased from 100 to 200 mg/dl.

Conclusions:

The net metabolic effect of insulin is nonlinear across the BG range and is amplified in hypoglycemia and dampened in hyperglycemia. Most importantly, the BG lowering per unit of insulin is accelerated when falling into hypoglycemia. The understanding of the accelerated risk for hypoglycemia with falling glucose levels will help the design of more robust hypoglycemia prevention and detection systems.

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Abbreviations: (BG) blood glucose, (GCRC) General Clinical Research Center, (HbA1c) hemoglobin A1c, (IE) insulin effectiveness, (IS) insulin sensitivity, (T1DM) type 1 diabetes mellitus

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