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ORIGINAL ARTICLES

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

Alice Chan, M.S.,[1] Lutz Heinemann, Ph.D.,[2] Stacey M. Anderson, M.D.,[1] Marc D. Breton, Ph.D.,[1] and Boris P. Kovatchev, Ph.D.[1]

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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Author Affiliations: [1]University of Virginia Health System, Charlottesville, Virginia; and [2]Profil Institut für Stoffwechselforschung GmbH, Neuss, Germany

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

Keywords: insulin effectiveness, net metabolic effect of insulin, nonlinearity, type 1 diabetes mellitus

Corresponding Author: Alice Chan, Diabetes Technology Center, University of Virginia Health System, P.O. 400 888, Charlottesville, VA 22908-4888; email address alicechan@virginia.edu

Introduction

Insulin therapy in patients with type 1 diabetes mellitus (T1DM) aims at providing enough insulin to cover basal requirements during the night and between meals and reduce glycemic excursions resulting from meals. To achieve optimal metabolic control, the dosage of insulin must be carefully adjusted individually, as the same dose of insulin has different effects on different patients or even within the same person. The ability of insulin to enhance blood glucose (BG) lowering is therefore related to a person's insulin sensitivity (IS). The many methods developed to assess IS generally correlated well and have shown that IS can be considered constant in the normoglycemic range.[1,2]

However, the IS may be different at low or high BG levels. For example, glucose toxicity refers to the impairment of insulin secretion and development of insulin resistance caused by sustained hyperglycemia.[3–5] This phenomenon is seen, for example, in obese patients with pre-type 2 diabetes mellitus whose insulin secretion has already reached a maximal level to compensate for insulin resistance,[5] but also in T1DM patients.[6] Similarly, to sustained hyperglycemia, acute hyperglycemic episodes also lead to attenuated insulin action. The saturation of the whole-body glucose uptake at higher BG levels has been long observed and confirmed with various levels of plasma insulin.[7–11]

While the nonlinearity of insulin action has been repeatedly observed at hyperglycemic levels of BG, very few studies have examined the effect of insulin in hypoglycemia. The linearity of the glucose uptake for a BG level as low as 60 mg/dl was assumed by Gottesman and colleagues[7] and was confirmed by Verdonk and associates[12] in healthy patients through euglycemic glucose clamps performed within the normal range of plasma insulin and BG ranging from 50 to 165 mg/dl. The effect of insulin on glucose uptake at low BG levels in T1DM patients has not been studied. It was suggested by Kovatchev and coworkers[13] that the action of insulin might be nonlinear in hypoglycemia. Their proposed nonlinear model, which assumed insulin action to be inversely proportional to glucose levels and proportional to plasma insulin concentration, was able to reproduce the glucose traces of T1DM patients undergoing a euglycemic hyperinsulinemic glucose clamp followed by a decrease of BG to moderate hypoglycemic levels.

The aim of the analysis presented in this article was to evaluate the effect of insulin on glucose absorption in T1DM patients at low and high BG levels through two separate studies. Based on the insulin net metabolic effect on glucose uptake, we define the insulin effectiveness (IE), a metric that evaluates the ability of one unit of active insulin to lower BG as a function of the current BG level.

Methods

The insulin net metabolic effect was assessed in hypoglycemia through a first study and in hyperglycemia through a second study.

Study 1: Hyperinsulinemic Euglycemic and Hypoglycemic Glucose Clamp

The study was approved by the University of Virginia Internal Review Board and performed at the University of Virginia General Clinical Research Center (GCRC). Written informed consent was obtained from all subjects. Eighteen hyperinsulinemic euglycemic and hypoglycemic glucose clamp studies were performed on 12 patients with T1DM (age 40 ± 10 years, body weight 82 ± 12 kg, hemoglobin A1c [HbA1c] 7.7 ± 1.9%). The clamps performed on the same subject were done at least six months apart from each other, which allowed us to consider them independent. Long-acting insulin was discontinued 60 h prior to the clamp procedure, and intermediate-acting insulin was discontinued 36 h prior to the clamp procedure. Only short- or rapid-acting insulin was allowed on the day of the admission. Subjects were admitted to the University of Virginia GCRC on the evening prior to study. At 21:30, an overnight insulin infusion consisting of regular insulin (Novolin R, Novo Nordisk, Princeton, NJ) in 0.9% saline at a concentration of 1:1 was titrated to control the subjects' BG overnight between 100 and 150 mg/dl by sampling YSI plasma glucose every 30 min and adjusting the rate of insulin infusion as needed. This was discontinued at 08:30 the following morning at the initiation of the glucose clamp procedure.

At time 0 of the clamp, an insulin infusion was started via Harvard pump by a 20 mU/kg priming over 10 min followed by a constant 1 mU/min/kg infusion maintained for the next 150 min as described by DeFronzo *et al.*[14] Blood glucose was clamped at basal levels via a variable-rate infusion of 20% dextrose. After 150 min into the

clamp, the glucose concentration was lowered at a rate of 1 mg/dl/min to a nadir of 50 mg/dl using a previously validated hypoglycemic clamping technique to ensure steady descent into hypoglycemia. The glucose concentration was held constant at 50 mg/dl for 30 min and then increased back at a rate of 1 mg/dl/min to 90 mg/dl, where it remained for an additional 30 min. Blood samples for plasma insulin and plasma BG levels were taken throughout the study at intervals of at most 10 min.

The effect of insulin was assessed at the steady states of BG levels, namely, at 90 and 50 mg/dl. Moreover, as the plasma insulin was maintained constant throughout the study, we also examined the evolution of the effect of insulin while BG levels steadily drop into hypoglycemia (**Figure 1A**).

Study 2: Hyperglycemic Clamp

The study was performed by Solianis Monitoring in cooperation with the Profil Institute for Metabolic Research GmbH, Neuss, Germany. The study was approved by the local ethical review board and carried out according to the protocol of Helsinki. Written informed consent was obtained from all subjects. Fifteen subjects with T1DM were enrolled in the study (age 27 ± 6 years, body weight 76 ± 13 kg, HbA1c 6.9 ± 0.8%). Patients were admitted at the Profil Institute in the morning of the study day, and after a 2 h preparation period, the subjects were connected to an artificial pancreas (Biostator). During the run-in phase, BG was stabilized at 100 mg/dl via variable-rate infusion of glucose and/or insulin solution. The glucose concentration was maintained at 100 mg/dl for 1.5 h and then increased to 200 mg/dl. This hyperglycemic plateau was maintained for 1 h. The Biostator provided BG measurements every minute.

The study was originally designed to investigate the effect of glucose variations on charge carriers, particularly electrolytes, and not to examine the effects of insulin at high BG levels. For this reason, insulin infusion was not maintained constant throughout the study and plasma insulin concentrations not measured. Nonetheless, by estimating plasma insulin concentrations by means of published models of plasma insulin kinetics and by examining the insulin effect at steady-state of glucose levels only, namely, at 100 and 200 mg/dl (**Figure 1B**), we attempted to assess the change in IE at mild hyperglycemic BG levels.

Insulin Net Effect

When the level of plasma insulin is maintained constant, the law of mass conservation yields

$$V_g \frac{dBG(t)}{dt} = \left(EGP(t) - EGP_b\right) - \left(Rd(t) - Rd_b\right) + GIR(t), \quad (1)$$

where V_g represents the glucose volume of distribution in dl/kg, $GIR(t)$ is the glucose infusion rate at time t in mg/min/kg, $EGP(t)$ is the endogenous glucose production in mg/min/kg, and $Rd(t)$ is the glucose disappearance rate in mg/min/kg. The net effect of insulin on glucose level can then be expressed in mg/min/kg as the combination of the decrease of endogenous glucose production and the increase in glucose uptake both compared to their basal value:

$$\begin{aligned}\text{Net effect} &= \left(Rd(t) - Rd_b\right) - \left(EGP(t) - EGP_b\right) \\ &= GIR(t) - V_g \frac{dBG(t)}{dt}.\end{aligned} \quad (2)$$

We define the normalized insulin net effect as the net effect resulting from a single unit of active insulin $X(t)$.

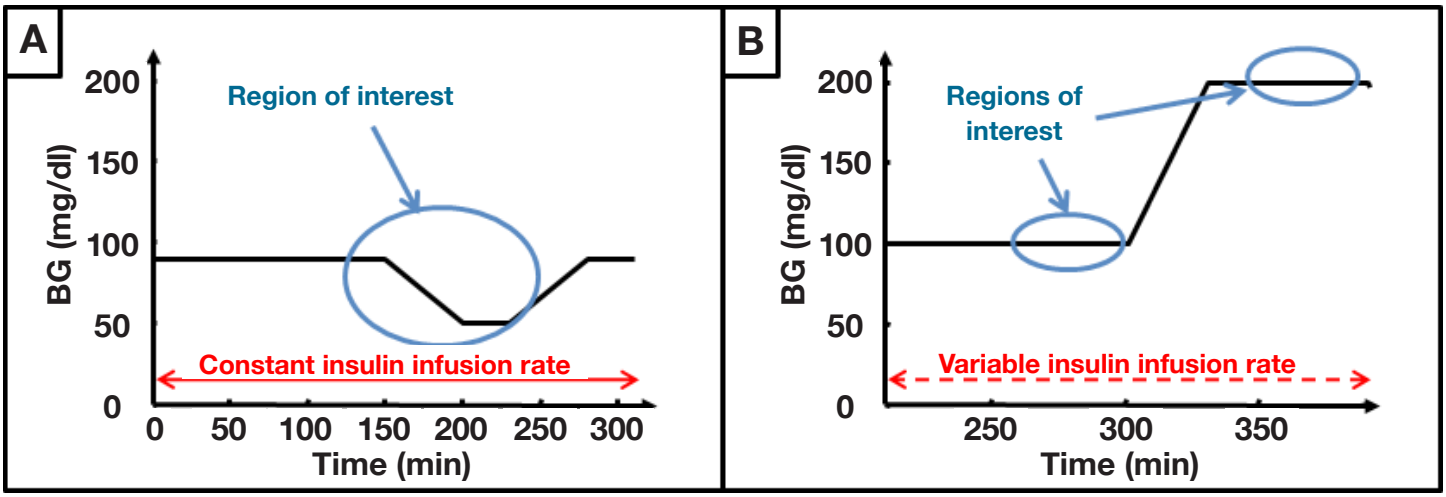

Figure 1. (**A**) Study 1: Hyperglycemic euglycemic and hypoglycemic clamp. The region of interest depicts the data used to assess the IE in hypoglycemia. (**B**) Study 2: Hyperglycemic clamp. The regions of interest depict the data used to assess the IE in hyperglycemia.

The active insulin $X(t)$, measured in pmol/liter, is assessed using the model published by Dalla Man and associates:[8]

$$\dot{X}(t) = -p_{2U}X(t) + p_{2U}\left(I(t) - I_b\right), \quad X(0) = 0, \tag{3}$$

where p_{2U} represents the rate constant of insulin action on the peripheral glucose utilization in min^{-1}, and $I(t)$ is the plasma insulin level at time t, with the subscript b denoting basal state. It is to be noted that, for the hyperinsulinemic clamp, X is constant throughout the region of interest.

In the first study, plasma insulin was directly measured, while in the second study, plasma insulin was estimated based on the intravenous insulin injection using the model depicted in **Figure 2** and described as

$$\begin{cases} \dot{I}_p(t) = -\left(m_2 + m_4\right)I_p(t) + m_1 I_l(t) + J(t), \; I_p(0) = I_{pb} \\ \dot{I}_l(t) = -\left(m_1 + m_3\right)I_l(t) + m_2 I_p(t), \; I_l(0) = I_{lb} \\ I(t) = \dfrac{I_p(t)}{V_i}, \; I(0) = I_b \end{cases}, \tag{4}$$

Where $I_p(t)$ and $I_l(t)$ are insulin masses at time t in plasma and liver, respectively, in pmol/kg; m_1, m_2, m_3, and m_4 are rate parameters in min^{-1}; $J(t)$ is the intravenous insulin infusion in pmol/kg/min; and V_i is the insulin volume of distribution. The population parameter values for T1DM patients are presented in **Table 1**.[8]

Insulin Effectiveness

As detailed earlier, many methods exist to quantify IS. All the methods, however, have in common that the ability of insulin to lower glucose levels is measured within normoglycemic glucose levels. In order to verify whether the effect of insulin is linear across the glucose range, a metric of the efficacy of insulin to lower glucose level that can take different values at different glucose

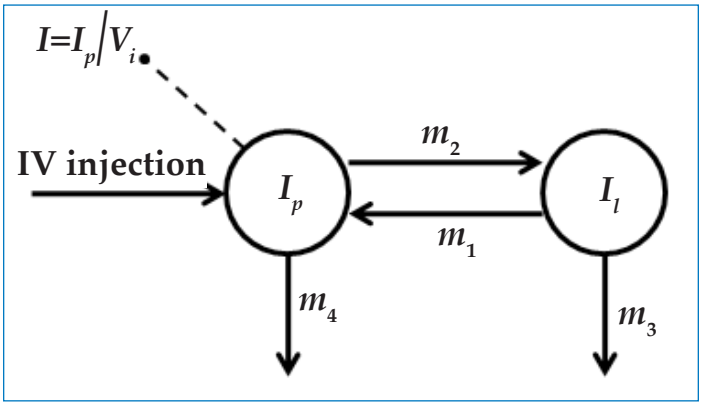

Figure 2. Representation of the insulin kinetics model.

Table 1.
Population Values of the Insulin System Model Parameter for Type 1 Diabetes Mellitus Patients

Parameter	Value	Unit
V_g	1.9	dl/kg
m_1	0.199	min^{-1}
m_2	0.284	min^{-1}
m_3	0.2985	min^{-1}
m_4	0.1136	min^{-1}
V_i	0.052	liter/kg
p_{2U}	0.0427	min^{-1}

levels needs to be defined. Thus we define the IE at BG_0, which we denote IE(BG_0), as the slope of the line that links the normalized insulin net effect at BG_0 and the normalized net effect extrapolated to 0 mg/dl from the values obtained in normoglycemia:

$$\frac{\text{Net effect}\,(BG_0)}{X} = IE(BG_0) \times BG_0 + c_0, \tag{5}$$

where c_0 is the normalized net effect extrapolated to 0 mg/dl from the values in normoglycemia. The IE at BG_0 quantifies the drop of glucose level from BG_0 that is produced by a unit of active insulin and is expressed in mg/min/kg/(pmol/liter)/(mg/dl). If the insulin net effect is linear across the BG range, the IE takes the same value for any BG_0 and is equal to the IS obtained through the euglycemic glucose clamp procedure. Otherwise, IE(BG_0) increases when the net effect of insulin is enhanced compared to its effect in normoglycemia and decreases when its effect is attenuated (**Figure 3**). Thus IE(BG_0) assesses the ability of a unit of active insulin to lower BG given its current glucose level BG_0.

Subject-Specific Glucose Volume of Distribution

When the level of plasma insulin is kept constant, the continuity of the effect of insulin on glucose absorption can be used to determine the subject-specific glucose volume of distribution. As the insulin infusion was maintained constant in the first study only, we computed subject-specific volume of distribution for subjects of the first study and used the population value for subjects of the second study. The insulin net effect computed during and before the glucose steady-state at 50 mg/dl was used to determine the subject-specific volume of distribution of subjects in study 1:

$$\text{Net effect at steady state} = GIR(t)\Big|_{SS} - V_g \frac{d\text{BG}(t)}{dt}\Big|_{SS}, \tag{6}$$

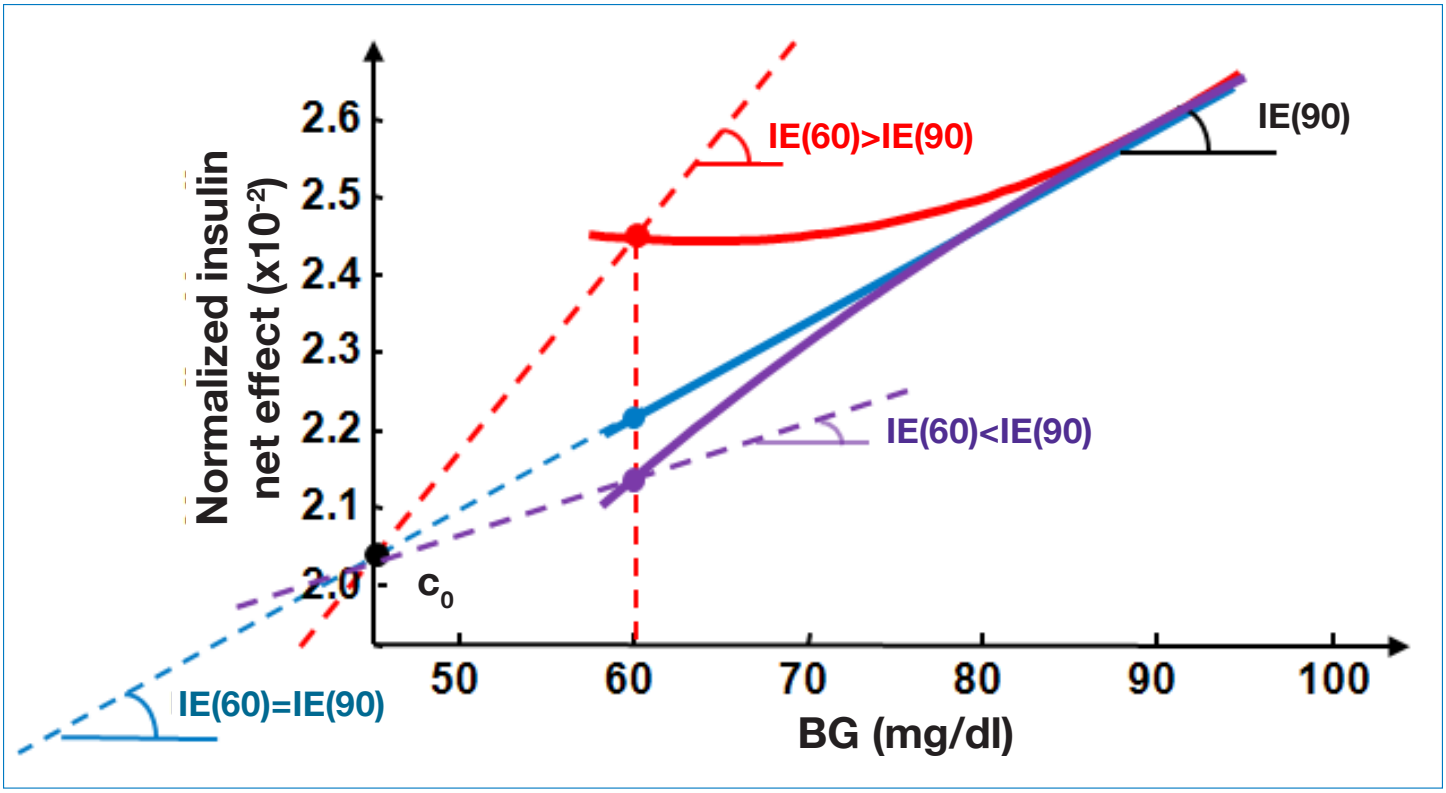

Figure 3. Insulin effectiveness calculation. First, the normalized net effect is extrapolated to 0 mg/dl from values in normoglycemia (c_0). Then IE(BG) is determined as the slope of the line between the normalized insulin net effect at that BG level and c_0. As illustrated for BG = 60 mg/dl, IE(BG) remains unchanged if the insulin effect is linear (**blue curve**), increases if the insulin effect is enhanced compared to normoglycemia (**red curve**), and decreases if it is dampened (**purple curve**).

$$\text{Net effect pre-steady state} = GIR(t)\big|_{preSS} - V_g \left.\frac{d\text{BG}(t)}{dt}\right|_{preSS}. \quad (7)$$

Since the insulin net effect before and during the glucose steady state at 50 mg/dl are equal, we infer the value of the glucose volume of distribution:

$$V_g = \frac{GIR(t)\big|_{preSS} - GIR(t)\big|_{SS}}{\left.\frac{d\text{BG}(t)}{dt}\right|_{preSS} - \left.\frac{d\text{BG}(t)}{dt}\right|_{SS}}. \quad (8)$$

The data were imported from Microsoft Office Excel files to Matlab R2007b (The MathWorks™), which was used to perform the data analysis.

Results

Insulin Effectiveness in Hypoglycemia

Blood glucose and plasma insulin concentration levels during the first study are shown as mean ± standard deviation in **Figure 4**. The glucose volumes of distribution obtained were 1.24 ± 0.51 dl/kg.

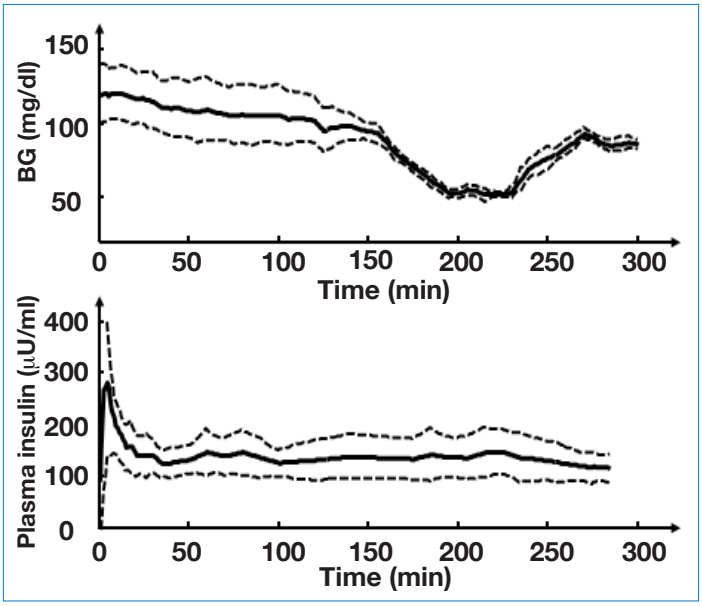

Figure 4. Blood glucose (**top**) and plasma insulin (**bottom**) concentration levels as mean ± standard deviation during study 1.

We computed the normalized insulin net effect during the steady states of euglycemia and hypoglycemia, as well as during the drop of BG levels from one steady state to the other one. Then the parameter c_0—insulin

net effect at 0 mg/dl extrapolated from values obtained in normoglycemia—was derived and the IE computed. The IE at 90 versus 50 mg/dl, 6.28 x 10^{-4} ± 1.70 x 10^{-4} versus 11.0 x 10^{-4} ± 4.53 x 10^{-4} mg/min/kg/(pmol/liter)/(mg/dl), respectively, were statistically different as assessed by a paired *t*-test (p = .015), meaning that the insulin effect is enhanced at 50 mg/dl compared to 90 mg/dl (**Figure 5**).

Moreover, the evolution of IE from the two steady states was assessed during the descent of BG into hypoglycemia. The IE increased by 75% as BG dropped from 90 to 50 mg/dl (**Figure 6**; **Table 2**).

Insulin Net Metabolic Effect in Hypoglycemia

The mean insulin net metabolic effect assessed during the hypoglycemic descent is not linear (**Figure 7**). In order to assess how much the net effect deviates from a linear net effect, a degree of nonlinearity d_x was introduced, defined as the difference between the actual net effect at BG = x mg/dl and its hypothetical value under the assumption of a linear net effect computed based on the effect in normoglycemia. This parameter measures the deviation of the insulin net effect from linearity. The degree of nonlinearity was different from 0 below 70 mg/dl ($p < 10^{-5}$), indicating that the insulin net effect is nonlinear in the hypoglycemic range. The actual mean insulin net effect is represented by the blue curve and the hypothetical linear insulin effect by the dotted curve in **Figure 7**.

Note that the insulin net effect computed at constant insulin infusion represents the amount of glucose that needs to be infused to keep BG at a given level. The insulin net effect does not decrease in a linear fashion, but more precisely, it first decreases as the glucose level drops from normoglycemia as would be expected but then increases when glucose level drops below 65 mg/dl. This was observed for all subjects but one. The net effect at 50 mg/dl was higher than at 65 mg/dl (= 1.03 x 10^{-4}), meaning that more glucose needs to be infused to keep BG constant at 50 mg/dl than at 65 mg/dl.

Insulin Effectiveness in Hyperglycemia

Blood glucose concentration levels during the second study are shown as mean ± standard deviation in **Figure 8**.

Because the insulin infusion was not maintained constant throughout the study, the population value of the glucose volume of distribution was used, and the insulin net effect was assessed at steady state of BG level only, i.e.,

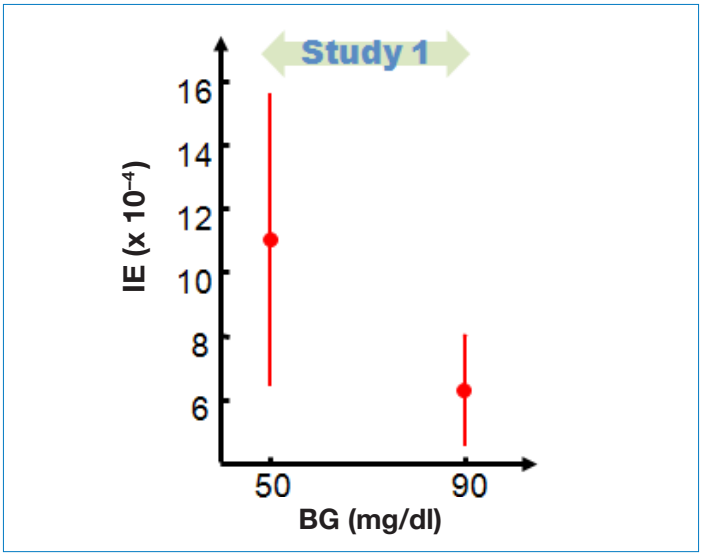

Figure 5. Insulin effectiveness for BG ranging at 50 and 90 mg/dl (mean ± standard error). Values were obtained from study 1 at steady states of BG levels. Insulin effectiveness is expressed in mg/min/kg/(pmol/liter)/(mg/dl).

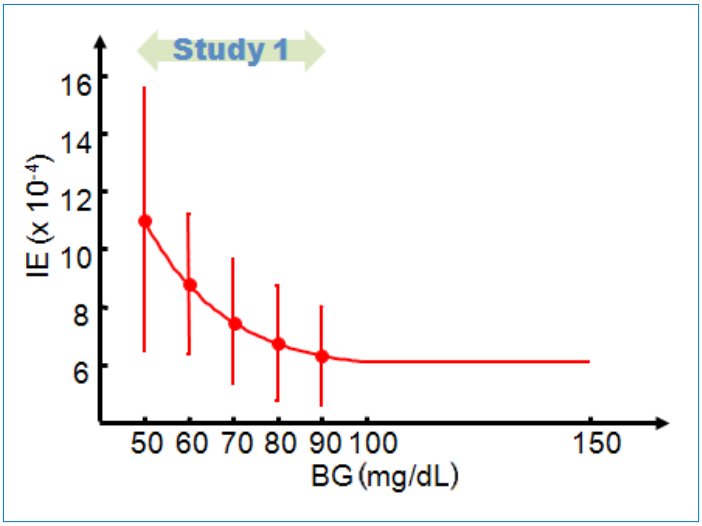

Figure 6. Insulin effectiveness for BG ranging from 50 to 150 mg/dl (mean ± standard error). Values were obtained from study 1 for BG from 50 to 90 mg/dl and extended to 150 mg/dl, where the IE is constant. Insulin effectiveness is expressed in mg/min/kg/(pmol/liter)/(mg/dl).

Table 2.
Insulin Effectiveness—Expressed in mg/min/kg/(pmol/liter)/(mg/dl)—at Various Blood Glucose Levels

BG [mg/dl]	IE (x 10^{-4})	Error (x 10^{-4})
90	6.28	1.70
80	6.71	2.00
70	7.45	2.14
60	8.74	2.42
50	11.0	4.53

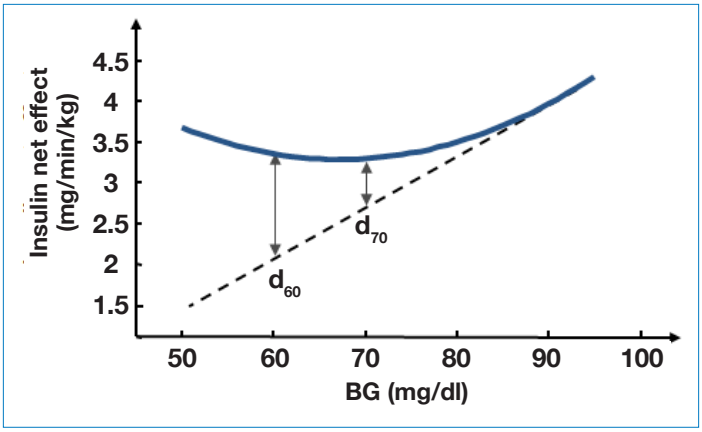

Figure 7. Insulin net effect at decreasing BG levels. The insulin net effect, representing the amount of glucose that needs to be infused to keep the BG constant at a given level, is nonlinear (**blue curve**). The degree of nonlinearity—the distance from the actual insulin net effect and the hypothetical value under assumption of a linear net effect (**dotted curve**)—is shown at BG levels of 60 and 70 mg/dl.

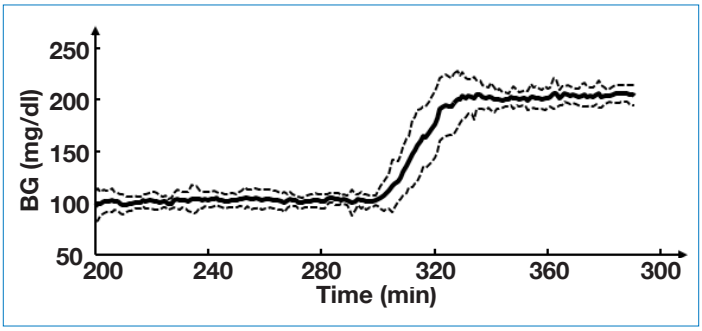

Figure 8. Blood glucose concentration levels as mean ± standard deviation during study 2.

at 100 and 200 mg/dl. The computation of IE requires an assessment of the slope of the insulin net effect in normoglycemia, which was not possible based on the values at 100 and 200 mg/dl only. Thus we used the IE obtained in normoglycemia from study 1 to derive the extrapolated insulin net effect at 0 mg/dl (c_0) required to compute the IE and then obtain an assessment at 200 mg/dl. The value of the IE obtained at 200 mg/dl was $5.45 \times 10^{-4} \pm 0.82 \times 10^{-4}$ mg/min/kg/(pmol/liter)/(mg/dl), representing a decrease of 10% compared to normoglycemia (**Figure 9**). As no data points were available between the two values, the shape of IE(BG_0) was hypothesized between 150 and 200 mg/dl. Although errors due to the estimation of plasma insulin concentrations might affect the quantification of IE, the small decrease of IE(BG_0) observed at 200 mg/dl brings some insight as to how much IE can change at a mild hyperglycemia and is in agreement with the clinical knowledge that the efficacy of insulin decreases in hyperglycemia and with the saturation of glucose uptake during acute hyperglycemia observed in several studies.

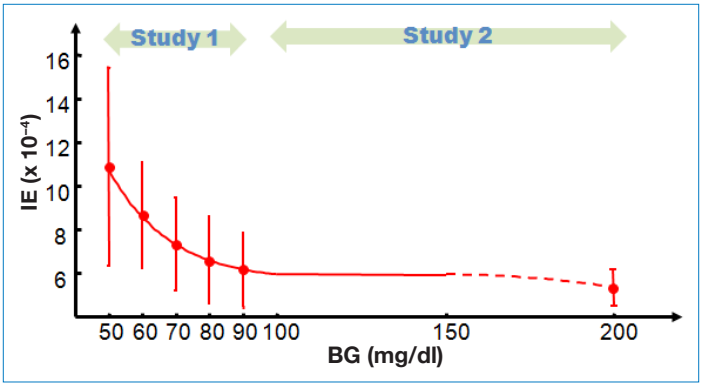

Figure 9. Insulin effectiveness for BG ranging from 50 to 200 mg/dl (mean ± standard error). Values were obtained from study 1 for BG from 50 to 90 mg/dl, extended to 150 mg/dl, where the IE is constant, hypothesized between 150 and 200 mg/dl (**dashed curve**) and obtained from study 2 at 200 mg/dl. Insulin effectiveness is expressed in mg/min/kg/(pmol/liter)/(mg/dl).

Discussion

The IE indicates the glucose lowering that a unit of active insulin can achieve at a given BG level. In normoglycemia, the IE matches the IS as defined by DeFronzo *et al*.[14] during a hyperinsulinemic euglycemic glucose clamp and is essentially linear. Our analysis showed that the effect of insulin is not linear across the BG range; it is dampened at higher glucose levels and enhanced at lower BG levels. The IE increased by 75% at 50 mg/dl compared to normoglycemia, meaning that, when BG drops below normoglycemia, the effect of insulin is amplified, causing BG levels to drop even faster and thus accelerating the risk for hypoglycemia. On the contrary, IE decreased by 10% at 200 mg/dl compared to normoglycemia. Although the latter assessment is based on estimated plasma insulin levels, the result suggests that, as the effect of insulin is attenuated at high BG levels, more insulin is needed to bring the patient's BG back to normoglycemic levels, which agrees with clinical knowledge. Maintaining BG within the safe range is thus a challenge for T1DM patients as, on one hand, the risk for hypoglycemia accelerates with falling BG levels and, on the other hand, bringing BG into normoglycemia from hyperglycemia is impeded by the decreased effectiveness of insulin.

The positive feedback loop generated by the increased glucose uptake during acute hypoglycemia seems to go against a natural autoregulation in health, and the pathway of the observed increase in sensitivity at low BG levels remains to be determined. Nonetheless, the observed increase of the IE in hypoglycemia could not be an artifact of counterregulation; a counterregulatory response would compensate for the effect of insulin in glucose lowering and would thus mean that the IE was

actually underestimated. Moreover, our measurements of epinephrine concentration every 10 min showed that none of the subjects exhibited epinephrine counterregulation for BG levels above 65 mg/dl. And below that level, even with an epinephrine response, we still observe an increase in the IE.

The assessment of the insulin net effect is based on changes in whole-body glucose uptake and endogenous glucose production. Although part of the observed changes might be insulin-independent, it has been shown that, under hyperinsulinemic conditions, skeletal muscles are the major sites of glucose disposal,[9,15] meaning that the IE defined from the insulin net effect is a good approximation of the ability of insulin to lower glucose levels. In this study, we had no means to separate insulin-dependent and insulin-independent effects, but regardless of that limitation, the observed nonlinearity of the insulin effect emphasizes how the risk for hypoglycemia accelerates when BG drops below normoglycemic levels.

In the first study, the insulin net effect was assessed at two levels of BG steady state and during the descent into hypoglycemia at a rate of 1 mg/dl/min. While the direct descent into hypoglycemia is similar to an actual drop of BG in a T1DM patient, the assessment of the change in IE during a multistep clamp allowing for steady states at progressively lower BG levels would be of interest. Besides, as the observed amplification of the insulin effect in hypoglycemia might depend on the rate of glucose descent, repeating the experiment with different rates of descent, combined with different levels of plasma insulin, would provide a more complete picture of the increased insulin effect in hypoglycemia. From glucose profiles observed in T1DM patients, a rate of descent of the glucose level of 1 mg/dl/min is realistic;[16] therefore, the variation of the IE in hypoglycemia for a 1 mg/dl/min rate of descent of the glucose level still provides a new understanding of the risk for hypoglycemia associated with insulin therapy. The nonlinear effect of insulin may provide a better understanding as to why hypoglycemia is difficult to control and still remains the major barrier to normoglycemia.

Continuous glucose monitoring systems have enabled the development of automated real-time assessment of the risk for hypoglycemia. This risk assessment is used to detect imminent hypoglycemia and either warn the user or, if coupled with an insulin pump, reduce or stop insulin delivery. Although these systems are becoming more sophisticated with the addition of algorithms that predict future BG levels[17–20] and inclusion of modern risk measures,[21] none of them uses the nonlinearity of the insulin effect that we believe would increase both accuracy and robustness of hypoglycemia detection and prevention systems.

Conclusions

This work provides an additional insight to the difficulty for T1DM patients to maintain normoglycemia through insulin therapy; the insulin net effect appears to be nonlinear across the therapeutically relevant range of BG. We defined IE as the ability of insulin to lower BG per unit of active plasma insulin at a particular BG level and observed that the IE increased in hypoglycemia and decreased in hyperglycemia. Consequently, maintaining normoglycemia is impeded by the accelerated risk for hypoglycemia with falling glucose levels. We believe that hypoglycemia detection and prevention systems could be improved with the inclusion of the nonlinearity of insulin effect across the BG range.

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