Understanding insulin and nutrition administration in glycemic control with the right side of the brain

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Research

Keywords: Critical care, nutrition, insulin, glycemic control, insulin sensitivity, insulin saturation, intensive care

Posted Date: September 22nd, 2020

DOI: https://doi.org/10.21203/rs.3.rs-75542/v1

Abstract

Background

Critically ill patients frequently experience stress-induced hyperglycaemia, leading to increased morbidity and mortality. Glycaemic control (GC) with insulin therapy alone has proven difficult, due to significant inter- and intra- patient variability in response to insulin therapy. This study reviews the problem and analyses the impact of physiological dynamics and patient variability on outcome glycemia.

Methods

A graphical model of metabolic dynamics is used to analyse the impact of fundamental glucose flux dynamics on insulin and nutrition administration in the context of maintaining a glycemic goal. It is used to delineate the limits of ability in controlling insulin and/or nutrition administration to achieve safe, effective glycemic control in critical illness in the presence of low insulin sensitivity and high insulin sensitivity variability.

Results

Insulin saturation limits insulin-mediated glucose uptake. At low insulin sensitivity, maintaining a glycemic target level requires reduced nutrition administration due to saturated insulin-mediated glucose uptake. Metabolic insulin sensitivity variability leads to insulin-mediated glucose uptake variability, requiring reduced nutrition administration at low insulin sensitivity and higher insulin doses to mitigate the risk of hypo- and hyper- glycemia.

Conclusions

This work reviews the clinical glycemic control problem using a graphically-based physiological analysis to show the need to control nutrition administration, along with insulin, to achieve safe, effective control. These reductions are necessary for highly insulin resistant patients, a condition typically occurring early in ICU stay. Glycemic control should directly control nutrition in addition to insulin to optimise all avenues of glucose flux and thus ensure safe, effective glycemic control.

1.0 Background:

Hyperglycemia is prevalent in critical care, caused by a complex interaction of multiple feedback loops immune, inflammatory, and counter-regulatory responses, and high blood glucose itself [1-4]. It is exacerbated by unsuppressed endogenous glucose production [1-3,5], medications [6], and high exogenous nutrition delivery [7]. In addition, suppression/loss of pancreatic insulin secretion [1-3,5], and loss of sensitivity to insulin, result in reduced insulin-mediated glucose uptake [8,9]. Hence, significant

hyperglycemia arises from reduced insulin-mediated glucose uptake, combined with enhanced endogenous and exogenous glucose delivery. Whether hyperglycemia is a beneficial evolutional response or glycemic control is harmful in the critically ill are both debated [2,10-14].

However, there are strong associations between the resulting blood glucose level and overall glucose variability with mortality [15-22] and a range of physiological responses [4,23,24]. Poor glycemic control leading to hypoglycemia is also linked with mortality [20,25-27]. In contrast, safe, effective control with high time in intermediate glycemic bands is associated with reduced mortality [28-33]. There is thus a need for safe glycemic control, which is difficult given high inter- and intra- patient variability in response to insulin and nutrition [8,9,19,22,34-36]. Control quality must also be consistent over time and most (or all) patients to achieve the potential benefits [37]. However, very few studies achieve this level of safe, consistent control [38-41].

Glycemic control is an appearance/clearance balance problem. Glucose levels result from the net combination of carbohydrate appearance and (primarily) insulin-mediated uptake. However, saturation of insulin action at high doses is almost always overlooked, where for doses over 6-8 U/h, any extra insulin has little or no impact [42,43]. While 6-8U/hour rates may be uncommon in outpatient diabetes, it is more common in critical care [44]. Thus, unlike glucose appearance, insulin action insulin-mediated uptake has an upper limit, which is more frequently encountered in critical care. Saturation of insulin action has implications for clinical choices on nutrition delivery, and thus glucose uptake, if the appearance/clearance balance is to be maintained – an often overlooked fact in clinical protocols.

This article uses a graphical model demonstrate the problem, delineate the impact of these dynamic interactions on how safe, effective control might be achieved for all patients.

2.0 Methods:

2.1 Fundamental Dynamics:

Figure 1 shows the fundamental metabolic physiological dynamics considered [45,46], including primary routes of glucose appearance and delivery, insulin appearance and delivery, and their uptake and use leading to a net blood glucose level. A directly related mathematical model in [46] is validated in clinical glycemic control [47-50], insulin sensitivity testing [51-54], and virtual patients [55-57]. For this analysis, time-varying and steady state levels of insulin (plasma $I(t)$ leading to interstitial $Q(t)$ à Q_{SS} in steady state), total nutrition ($P(t)$ à P_{SS}) and glucose level ($G(t)$ à G_{SS}) are used. Insulin sensitivity, SI, captures patient-specific ability for insulin mediated glucose uptake.

2.2 The impact of Insulin Saturation:

Interstitial insulin, $Q(t)$, is the effective insulin for removing glucose, where insulin action can saturate as insulin dose increases. Insulin saturation has been directly assessed clinically, and observed in reduced rises in glucose infusion rates as insulin infusion rates increase in stepped euglycemic clamp studies and

critically ill patients [42,43,58-76]. Insulin saturation limits insulin-mediate glucose uptake and is an important effect in the glycemic control of highly resistant (low *SI*) critically ill patients.

In particular, at steady state, Q_{SS} approaches a maximum value, Q_{MAX}, typically achieved at infusion rates of 6-8 U/hour in adults [42,43]. Thus, for a given insulin sensitivity level, *SI*, the maximum rate of insulin-mediated glucose removal is limited. In turn, to match glucose appearance and removal, and thus maintain constant blood glucose, the exogenous nutrition rate is also limited to some P_{MAX}. Thus, as insulin sensitivity falls, Q_{SS} à Q_{MAX} and P_{SS} à P_{MAX}, where above P_{MAX} glucose levels will rise, even with more insulin. Insulin saturation thus connects insulin delivery and nutrition delivery, and define limits on each if a given glycemic level is to be maintained. Importantly, most clinical protocols ignore nutrition rates in glycemic control [44,77-79]. However, this linkage shows how high nutrition delivery can lead to hyperglycemia in the presence of insulin saturation, when insulin resistance is high (low *SI*).

2.3 A Graphical Model of Glycemic Control and Physiological Dynamics:

Sections 2.1 and 2.2 define all necessary terms for a graphical model of how they interact (*SI*; Q_{SS} and Q_{MAX}, and P_{SS} and P_{MAX}). This model is shown in **Figure 2**, including insulin and nutrition inputs with a potential "max" value, determined by patient-specific insulin saturation and insulin sensitivity, *SI*, levels. *SI* is defined from low (very resistant) to high. In combination, *SI*, current glucose concentration, G, and effective insulin, *Q*, yield a variable glucose removal (**Figure 2**, lower left) described by the width of the arrow added to a fixed uptake by the brain and other non-insulin mediated tissues [45,80-88].

Hence, for a given *SI* (e.g. Medium in **Figure 2**), a glucose target (G Target in **Figure 2**) is met using insulin to manage a given nutrition input. If *SI* falls, glucose will rise without changing insulin dose. Equally, if *SI* rises, the insulin required to hold a given glucose level, for the same amount of nutrition, will fall. These behaviours when *SI* changes are shown in **Figure 3** for fixed insulin and nutrition, where glucose rises or falls in accord, fully defining the model.

3.0 Results:

3.1 The impact of Insulin Saturation:

Figure 4 shows the steady state at given insulin and nutrition doses below their (related) maximum values. In this case, nutrition might be increased, if desired, compared to a goal feed level or any other metric, and insulin could be increased to maintain steady state glycemia at $G_{SS} = G_{TARGET}$.

Figure 5 shows a highly insulin resistant patient with lower *SI* than **Figure 4**, with insulin increased to its maximum and Q_{SS} à Q_{MAX}. To maintain a desired glycemia, nutrition is limited to P_{MAX}, which represents the maximum flux of glucose into (and out of) the blood at which $G_{SS} = G_{TARGET}$ can be maintained. Any higher nutrition input ($P_{SS} > P_{MAX}$) would raise steady state glucose (G_{SS}) above the target, as insulin saturation limits insulin-mediated uptake to a maximum level at a given insulin sensitivity (*SI*), which is

shown in **Figure 6**. Thus, Figures **5-6** show how insulin resistant patients with relatively lower *SI* will have to receive restricted nutrition inputs to maintain $G_{SS} = G_{TARGET}$.

In summary, insulin saturation limits effective insulin for insulin-mediated glucose removal. The lower a patient's insulin sensitivity (more resistant), the lower the insulin-mediated glucose removal possible at this upper limit. As such, relatively higher nutrition for this patient will result in higher steady state glycemia above target. Thus, above the Q_{SS} à Q_{MAX} limit (**Figure 5**), nutrition inputs must be reduced to avoid hyperglycemia (**Figure 6**) beyond a given target level, showing an interaction of physiological dynamics on an often ignored clinical input in restricting glycemia to an intermediate range, which in turn defines a subset of the most insulin resistant (low *SI*) patient hours.

3.2 The Impact of Metabolic Variability:

ICU patients display significant intra-patient metabolic, and thus outcome glycemic, variability [8,37,89]. **Figure 7** the outcome effects of variability in insulin sensitivity, . This metabolic variability and/or uncertainty can move glycemia beyond clinically set or desired hyperglycemic (for falling *SI*) or hypoglycemic (for rising *SI*) limits as changing *SI* changes insulin-mediated glucose uptake. The resulting glycemic variability is associated with worsened outcomes [16,27,30,90].

Figure 8 shows how reducing nutrition can reduce and manage the width of glycemic variability, while also reducing insulin requirements. The key outcome is higher insulin and/or nutrition magnifies the glycemic variability arising from changes in *SI*, widening the range of possible blood glucose level outcomes in the presence of *SI* variability over time. Reducing the resulting glycemic variability thus reduces risk [16,30,31,33] and improves control. This dynamic interaction will affect patients on higher insulin doses more, who are generally those with lower *SI* and higher glycemic levels.

In summary, glycemic variability is a major hyper- and hypo- glycemia risk factor. Directly managing glycemic variability via reduced nutrition dosing for patients with low *SI* can reduce risk and improve outcomes.

4.0 Discussion:

4.1 Main Results: The impact of Insulin Saturation:

The analysis in **Figures 4-6** clearly shows the trade-off between nutrition delivery, insulin saturation, and control to a specified blood glucose level. If insulin action was unlimited, where more insulin resulted in more insulin-mediated glucose uptake, nutrition could be independently set and a specified blood glucose level achieved as part of any standard titration problem. However, insulin action and effect is saturated [42,43,58-76], and increasing insulin doses eventually have less to no effect, except to raise plasma and interstitial circulating insulin levels. Hence, insulin saturation limits insulin-mediated glucose uptake, in turn limiting the total possible carbohydrate delivery to maintain a specified blood glucose level (**Figure**

5), unless blood glucose is allowed to rise (**Figure 6**). Thus, there is a patient specific, variable upper limit of carbohydrate delivery, which is a function of the patient's insulin sensitivity (*SI*).

A high *SI* value indicates larger potential insulin-mediated glucose uptake is possible, and a low value a more resistant patient. Thus, highly insulin resistant patients, typical of ICU patients requiring glycemic control [1-3,5], are more likely to need lower nutrition delivery to maintain desirable glucose levels [91]. This outcome matches results showing lower mortality at reduced average nutrition delivery rates compared to current guideline rates [92-94], even though only a subset of more insulin resistant patients and/or patient hours might require such reductions from a typical goal nutrition delivery level.

Currently, nutrition delivery is most frequently set to local clinical standards for virtually all glycemic control protocols. Clinical insulin protocols are thus "carbohydrate blind", neither knowing nor accounting for nutritional intake [95,96]. To date, only the model-based STAR and eMPC protocols consider nutrition explicitly [97-100], and only STAR modulates nutrition delivery in addition to insulin [98-100]. STAR and eMPC also directly identify patient-specific *SI* using virtual patient models [101,102], and can thus manage the entire trade-off in **Figures 4-6** directly.

Clinical Impact. There are two clinical outcomes of **Figures 5-6**. The first is the clinical need to include nutrition delivery in glycemic management, whether or not it is controlled. The second is the clinical need to limit and optimise nutrition delivery for more insulin resistant (low *SI*) patients as a direct part of safely and effectively managing glycemia, where this restriction is increasingly seen as necessary in general [103,104]. As a result, model-based or similar methods to monitor insulin sensitivity (*SI*) directly could become more necessary to identify who, when, and how much nutrition should be reduced.

4.2 Main Results: The Impact of Metabolic Variability:

SI can vary significantly between and within critically ill patients [8,37,89]. **Figures 6-8** describe the impact of *SI* variability on glycemic outcome and safety, and demonstrate the potential need to manage nutrition delivery to mitigate hypo- and hyper- glycemic risk.

Figure 7 illustrates the risk of SI variability, where critically ill patients have significant variability in their hour-hour insulin sensitivity, particularly early in ICU stay [89,105]. Hypoglycemic risk from rising *SI* ( ) can result in moderate or severe hypoglycemia in up to 10% of hours in the first 1-3 days of stay, depending on insulin dose [106]. The width of the potential variation is a function of insulin dose and nutrition rate given, where blood glucose level, insulin dose, and nutrition rate together magnify uncertainty in *SI*. The implication is smaller insulin doses, which can require lower nutrition rates, result in lower glycemic variability (**Figure 8**). Hence, more insulin resistant patients (lower *SI)* (**Figures 4-5**), with high blood glucose and insulin (and/or nutrition) rates may benefit from short-term reduction of nutrition to reduce both glycemic level *and* variability, as shown **Figure 8**.

Clinical Impact. Inter- and intra- patient metabolic variability in insulin sensitivity can significantly change the glucose levels resulting from any given insulin dose. The more insulin resistant the patient, the larger

the insulin dose required, and thus the wider the resulting glycemic variability range resulting from changes in insulin sensitivity. Reducing nutrition, within clinically accepted ranges, is a means of managing this glycemic variability, and will be necessary for more resistant patients to mitigate avoidable hyper- and hypo- glycemic events resulting from metabolic variability.

Clinically, it is possible to quantify and thus account for this variability, creating an objective means to reduce hypoglycemic and hyperglycemic risk [89,105,107-110].

4.3 Limitations: Does Limiting Nutrition Reduce Total Nutrition Delivery?

Figures 4-6 illustrate the potential need to reduce or control nutrition delivery in managing glycemia patients with higher insulin resistance (lower *SI*). Nutrition delivery for the critically ill is an area with significant debate concerning the level of nutrition required, how much is practicable to deliver, delivery route, and the impact of macronutrients [92-94,104,111-121]. Recent analyses lean towards a staged approach, increasing nutrition delivery over ICU stay as patient condition improves, thus limiting nutrition delivery per protocol to lower than full or goal feed levels early in stay (e.g. [103,118,120]) when the greatest insulin resistance and variability most typically occur [8,37].

Figures 5-6 illustrate how insulin saturation limits insulin-mediated glucose uptake and thus limits the level of carbohydrate intake a patient can tolerate to avoid excessive hyperglycemia. The more insulin resistant the patient, the lower this value. Hence, at any given hour of stay, any given patient may be able to tolerate more or less carbohydrate nutrition intake than another otherwise similar patient, where a model-based *SI* value can differentiate such patients.

Currently, only the STAR protocol explicitly modulates insulin and nutrition to manage glycemic level and variability and risk due to Intra- and inter- patient metabolic variability [38,47,122]. Thus, the results in [91], showing mean nutrition during glycemic control met or exceeded leadin nutrition delivery over days 1-3 of ICU stay in a survey of 158 ICUs in 20 countries by Cahill et al [112], were surprising. Equally, a per-patient analysis showed a significant spread of maximum tolerated nutrition intake over the 221 patients (21,769 hours) in [91], where these patient-specific levels rose each day of ICU stay and faster than proposed in [103,118,120]. These results show how directly accounting for insulin sensitivity and insulin saturation, and its variability, can temporarily reduce nutrition delivery, but maximise overall nutrition delivery based on patient-specific tolerance, resulting in clinically very high levels of nutrition delivery despite controlling it to manage glycemia. More generally, limiting nutrition to improve glycemic control and minimise risk of glycemic variability does not have to limit total nutrition.

4.4 Clinical Takeaways:

The overall results show a relatively complex, often ignored, and difficult to measure trade-off. Highly insulin resistant patients are common and create the conditions where reducing nutrition is necessary. More succinctly, high and variable insulin resistance (low and variable *SI*) requires direct modulation and control of nutrition, in addition to insulin, to minimise the risk of excessive hyperglycemia and

hypoglycemia. It can also result in high levels of overall nutrition delivery over the first 3-5 days of ICU stay, despite temporary reductions. This outcome and approach require model-based or similar methods to monitor insulin sensitivity (*SI*) directly at the bedside to understand for whom, when, and how much nutrition should be reduced. Overall, controlling nutrition inputs to provide safe, effective and patient-specific glycemic control is as much about optimising nutrition as it is about glycemic control.

5.0 Conclusions:

Hyperglycemic critically ill patients are highly insulin resistant and highly variable. Glycemic control to intermediate or tighter ranges can improve outcomes, but is hard to achieve safely and effectively. This analysis presents a simple pictorial model to illustrate the trade-off between the saturation of insulin action and insulin-mediated glucose uptake, nutrition delivery, and resulting glycemia. It is used to show how highly insulin resistant patients, typical of hyperglycemic critically ill patients, can require reductions in nutrition delivery to maintain a given glycemic level. More specifically, it illustrates how any given patient has a maximum nutrition delivery rate they can tolerate, which, based on prior studies, is patient-specific and time varying, indicative of the significant metabolic inter- and intra- patient variability common in this cohort. Hence, nutrition control is a necessary aspect of managing the hyperglycemic critically ill patient, both reduction and augmentation.

Clinical takeaways include the need for nutrition modulation in response to patient-specific condition to mitigate the risk of excessive hyperglycemia and increased risk of hypoglycemia with increasingly high insulin doses. Equally, controlling nutrition inputs to provide safe, effective and patient-specific glycemic control is as much about optimising nutrition as it is about glycemic control. Emerging model-based methods of patient management and glycemic control offer the opportunity to implement these approaches into regular care.

6.0 List Of Abbreviations:

- GC = Glycemic Control
- ICU = Intensive Care Unit
- SI = Insulin Sensitivity
- DSI = Change in Insulin Sensitivity
- STAR = Stochastic TARgeted (glycemic control protocol)

7.0 Declarations:

Ethics approval and consent to participate: No clinical data was used in this analysis.

Consent for publication: No clinical data was used in this analysis.

Availability of data and materials: Data sharing is not applicable to this article as no datasets were generated or analysed during the current study.

Competing interests: The authors declare that they have no competing interests.

Funding: This study was supported by New Zealand National Science Challenge 7, Science for Technology and Innovation (#CRS-S3-2016), and the MedTech CoRE program funded by the New Zealand Tertiary Education Committee (#3705718).

Authors' contributions: All authors contributed to conception, design, and result interpretation. JGC carried out the main analysis. JLK had significant input to methodology and analysis. JGC and JLK wrote and revised the article in entirety, and approved the final manuscript.

Acknowledgements: Not Applicable.

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Figures

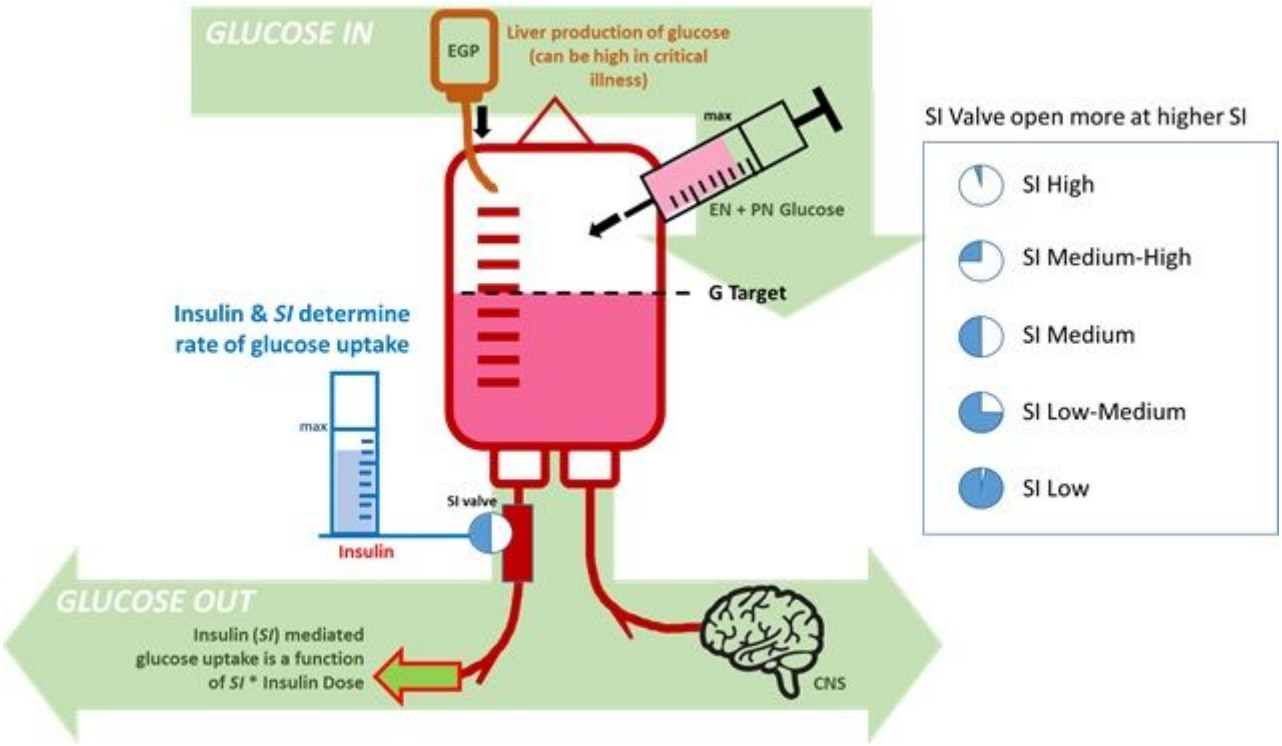


Figure 1

Model schematic showing the physiological compartments and clearances, as well as the appearance of exogenous insulin and carbohydrate, and their fundamental kinetic pathways. Insulin sensitivity (SI) captures the patient-specific rate of insulin-mediate glucose uptake for a given insulin level and can vary over time (hour to hour).

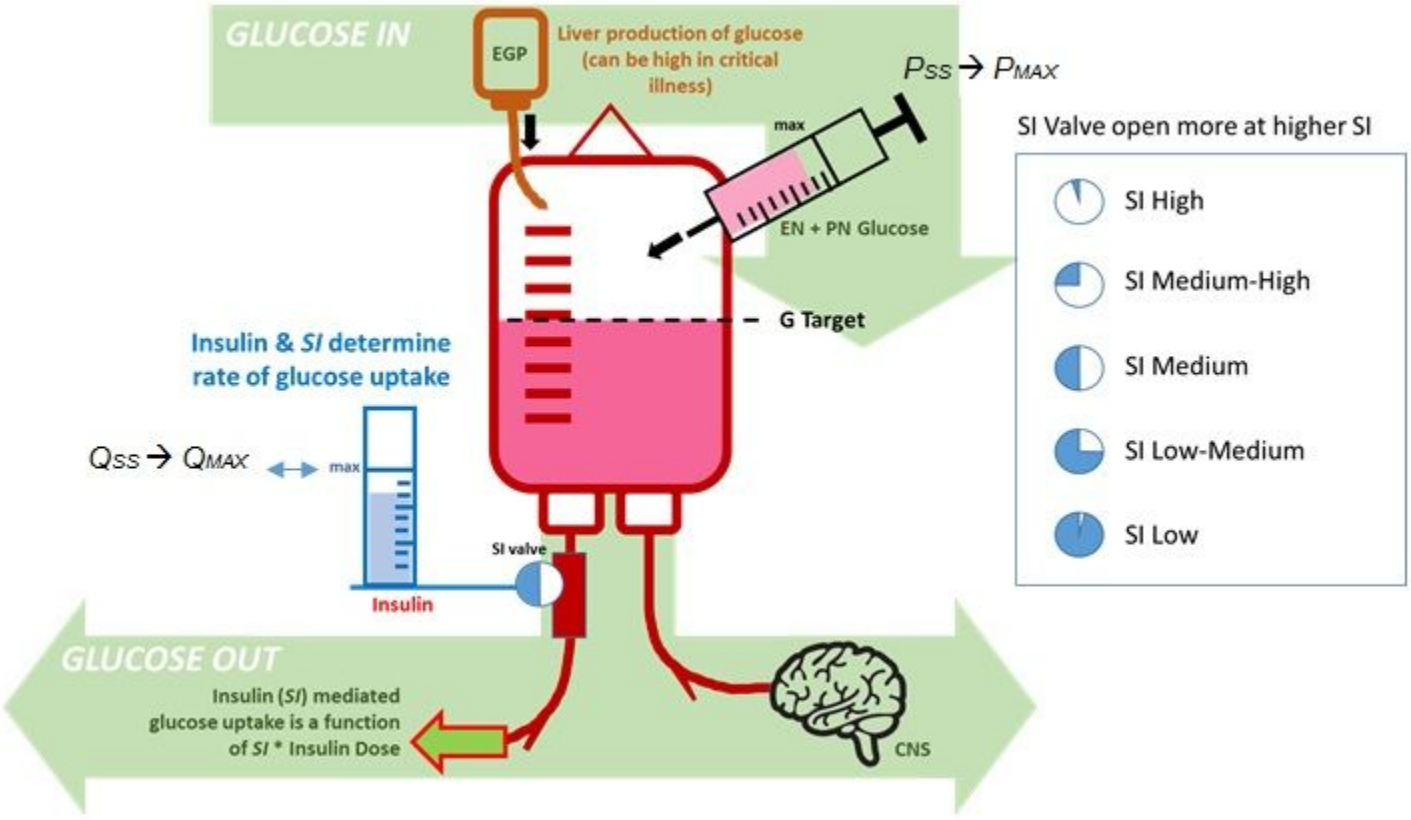


Figure 2

Graphical model used in this analysis, defining all fundamental glucose and insulin fluxes required to assess the impact of nutrition and insulin saturation. Maximum insulin administration is associated with QSS QMAX and maximum exogenous nutrition administration by PSS PMAX.

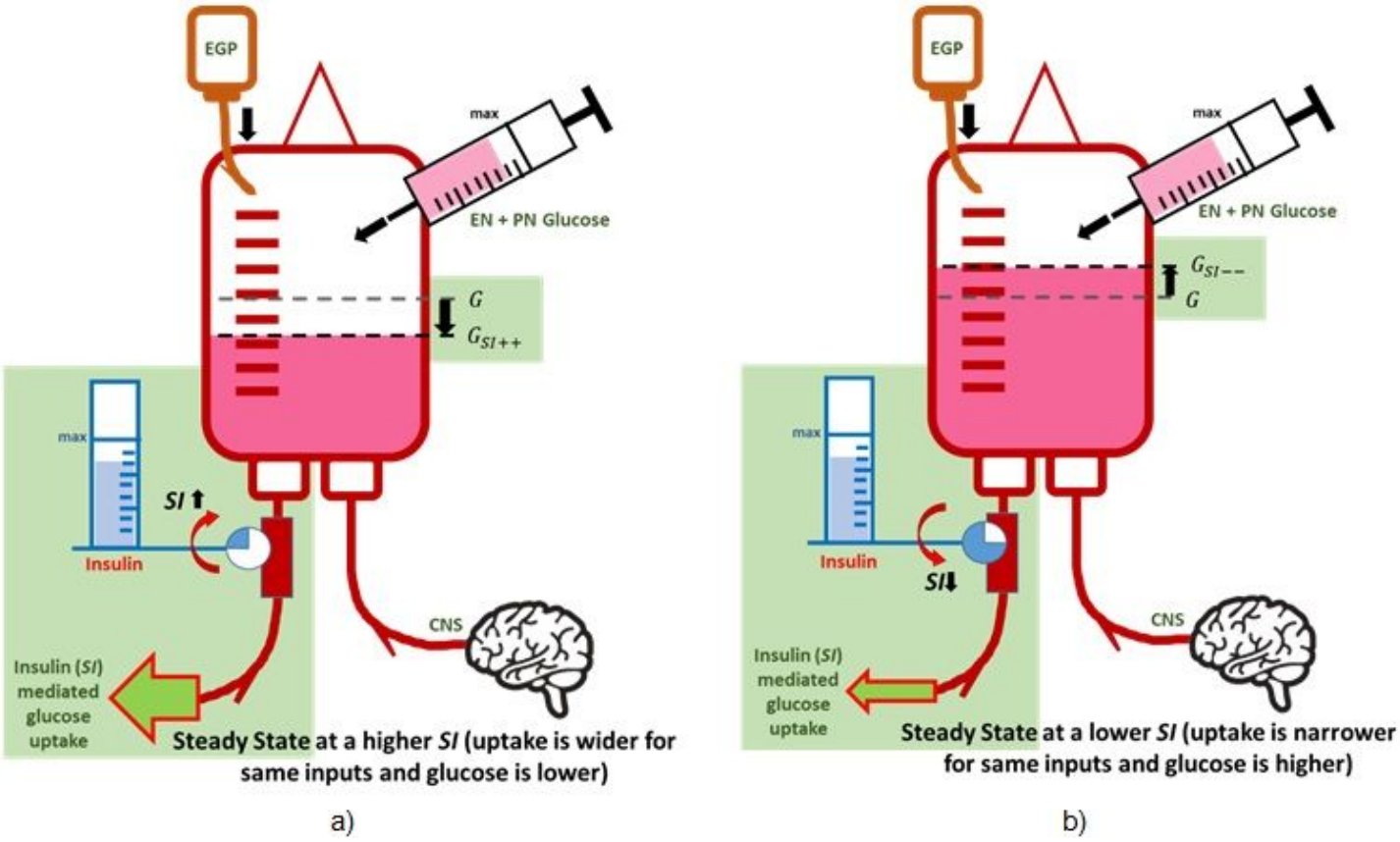


Figure 3

For fixed insulin and nutrition delivery in Figure 2, a) blood glucose falls if SI rises and outcome insulin-mediated glucose uptake arrow gets wider compared to Figure 2 (relative comparison), and b) rises if SI falls with narrower glucose uptake arrow. These changes demonstrate the basic mechanics and behavior of this graphical model used to demonstrate behaviour.

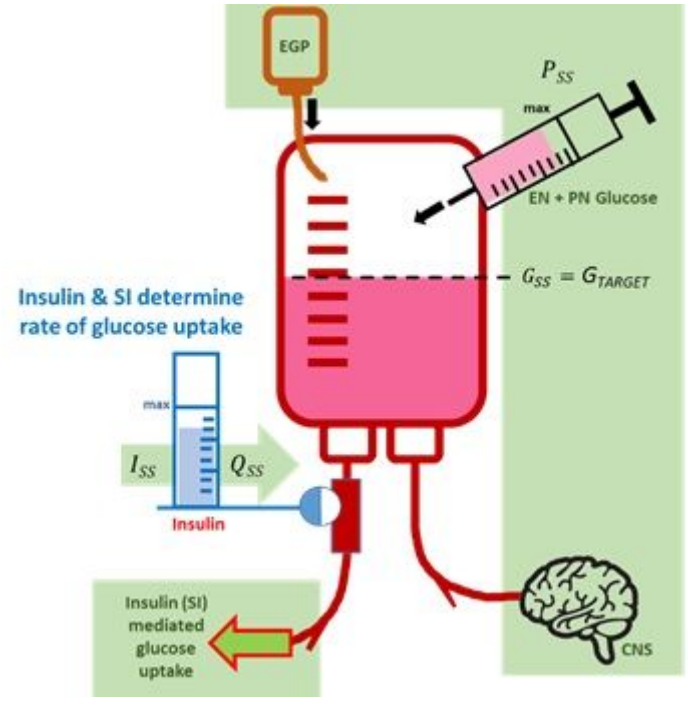


Figure 4

Steady state at insulin and nutrition inputs below their limited maximum values for a typical patient, and the resulting steady state glucose value GSS = GTARGET.

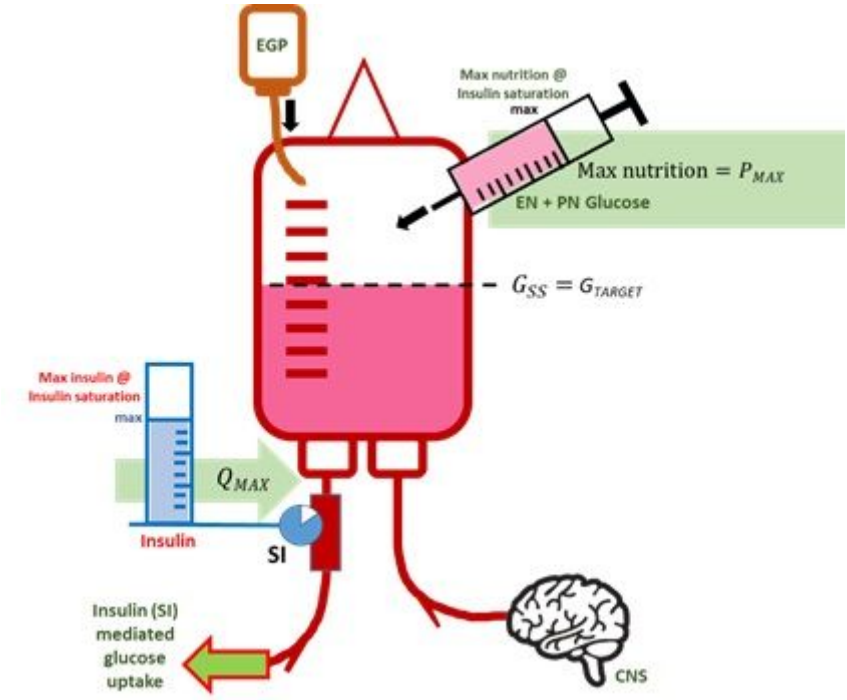


Figure 5

Steady state when insulin saturation limits effective insulin to QMAX and thus the total insulin-mediated removal is limited at Pmax. As a result, nutrition input to maintain the same steady state glucose level (GSS = GTARGET) is limited. Note SI is lower in this figure compared to Figure 4 (using Figure 2) for a highly insulin resistant patient.

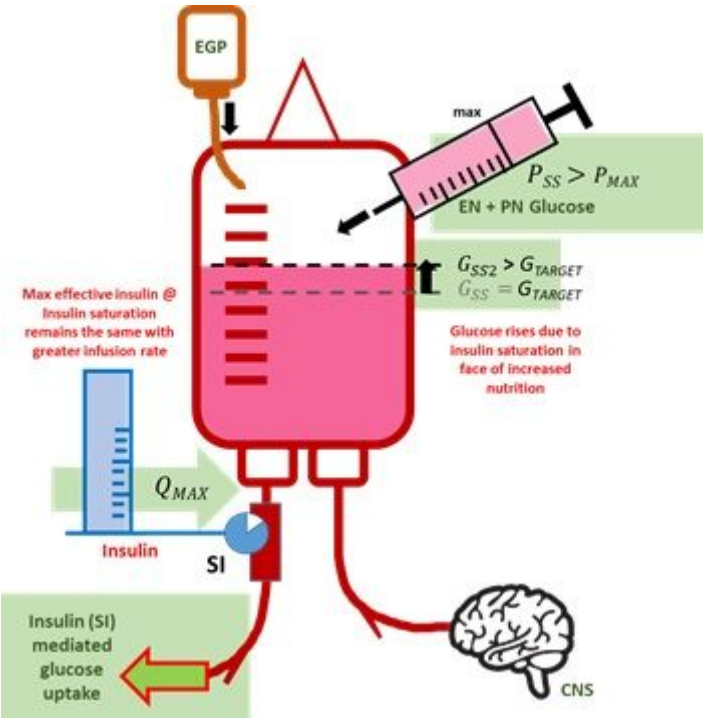
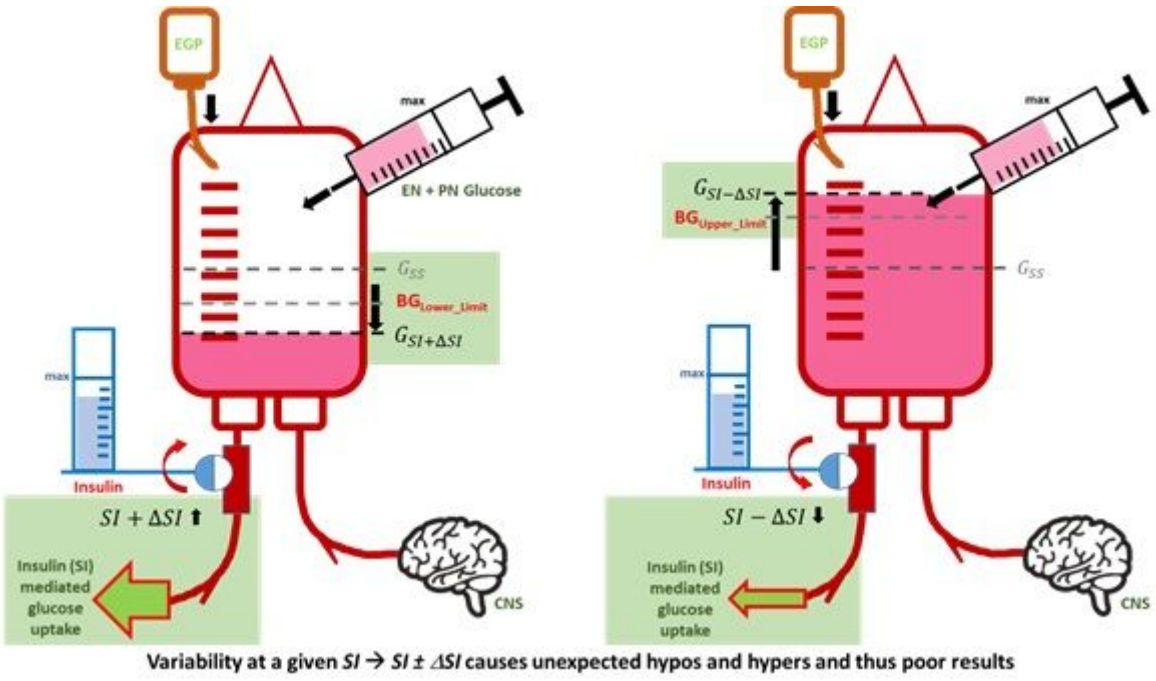


Figure 6

When nutrition is increased past the upper limit (PSS > PMAX) for the same patient as in Figure 4, the steady state glucose rises and because insulin is saturated in effect, the width of the glucose removal flux is the same as in Figure 4.



Variability at a given *SI* → *SI* ± *ΔSI* causes unexpected hypos and hypers and thus poor results

Figure 7

Variability in insulin sensitivity is common and causes significant variability in outcome insulin-mediated glucose flux as SI→SI±ΔSI, noting the wider arrow left for rising SI and more insulin-mediated glucose flux for a given insulin dose; and smaller arrow right for falling SI and increasing insulin resistance.

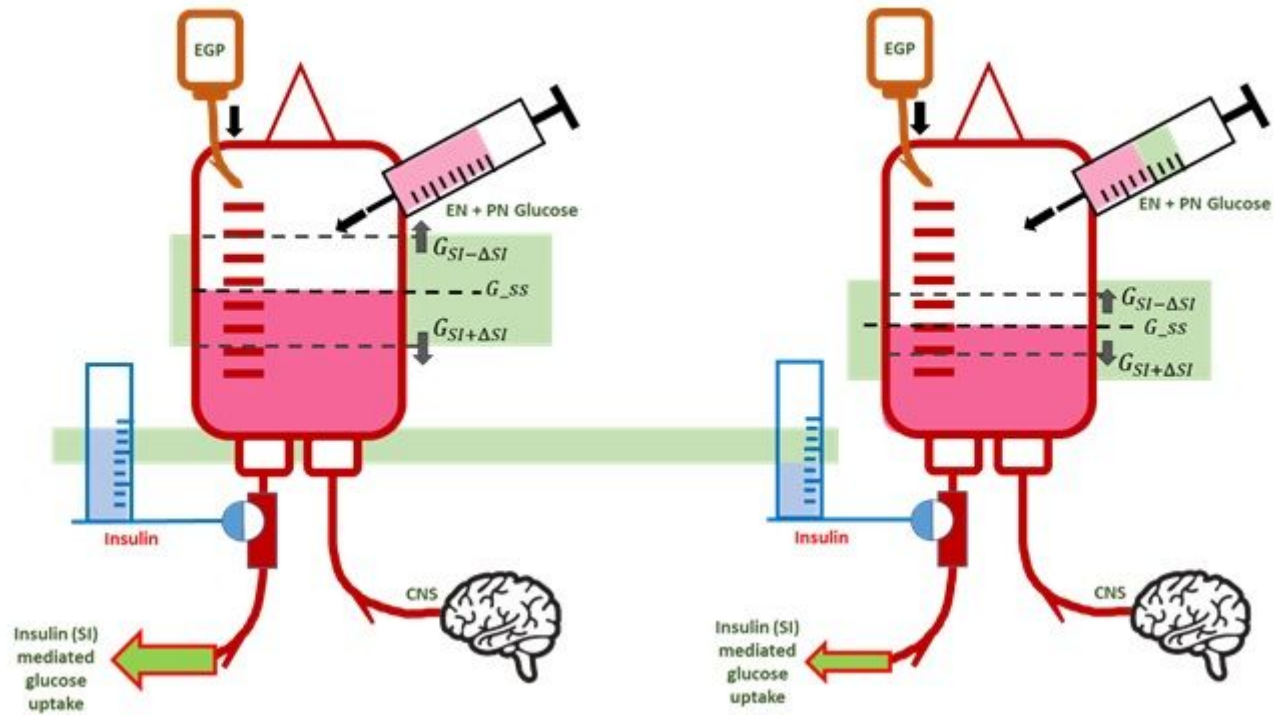


Figure 8

From left to right: Limiting or reducing nutrition inputs, at any given insulin sensitivity level, SI, can be used to reduce the range of variability, as well as concomitantly reducing the required insulin inputs.

Supplementary Files

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- GraphicalAbstract.jpg