Capacity of Infusion Lines for Insulin Adsorption: Effect of Flow Rate on Total Adsorption

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Abstract

Background: Insulin adsorption to clinical materials has been well observed, but not well quantified. Insulin adsorption reduces expected and actual insulin delivery and is unaccounted for in insulin therapy or glycemic control. It may thus contribute to poor control and high glycemic variability. This research quantifies the problem in the context of clinical use.

Method: Experimental insulin adsorption data from literature is used to calculate insulin delivery and total insulin adsorption capacities for polyethylene (PE) and polyvinyl chloride (PVC) lines at clinically relevant flow rates and concentrations.

Results: Insulin adsorption capacity decreased hyperbolically with flow rate for both PE and PVC, where low flow scenarios result in greater insulin adherence to infusion lines. When the infusion flow rate was halved from 1 to 0.5 mL/h, twice as much insulin adsorbed to the line. Insulin loss to adsorption resulted in up to ~50% of intended insulin not delivered over 24 hours in a low flow and low concentration context.

Conclusion: Material capacity for insulin adsorption is not constant, but increases with decreasing flow. Different materials have different adsorption capacities. In low flow and low concentration contexts, such as in neonatal or pediatric intensive care, insulin loss to adsorption represents a significant proportion of daily insulin delivery, which needs to be accounted for.

Keywords

insulin infusion, insulin adsorption, insulin binding, intensive care

Introduction

Insulin adsorption (binding) to material surfaces during clinical delivery has been well described, but not well quantified. First documented in the 1960s–1970s,^{1–5} it has recently returned to prominence with a second burst from the late 1990s to present.^{6–14} Importantly, while the phenomenon is well documented, no methods to quantify, predict, and thus manage this loss have emerged. Given the dangers of hypoglycemia^{15–17} and glycemic variability,^{18–20} as well as those of line blockages for wearable insulin pumps,^{21–23} it is a potentially significant gap with implications for modern precision insulin therapy systems.

Protein adsorption to delivery systems is a common phenomenon,^{24–27} where the degree of adsorption and its clinical significance depends on the drug of interest.^{25,26} The key problem with insulin adsorption is unaccounted for underdelivery of insulin. This adsorptive insulin loss is greatest within the first one to two hours of new insulin infusion line use, where typically only 20%–80% of the desired insulin dose is delivered.^{6–8,10} Insulin adsorptive loss is much more

significant where low concentrations and flow rates are used,^{6,7,10} as are commonly used in neonatal and pediatric intensive care units (NICU and PICU).

Protein adsorption itself is complex, often involving protein denaturing and/or aggregation.^{28,29} While adsorption and aggregation are different, but related, phenomena, surface adsorption is thought to provide conditions for later aggregation.^{30–32} Insulin is known to adsorb and aggregate more readily on hydrophobic surfaces compared to hydrophilic surfaces, with distinct phases.^{30,31} Insulin adsorption also depends on the surface hydrophobicity and surface roughness,³³ and occurs on glass^{1,34,35} and various types of plastic containers and delivery tubing,^{3,4,11–13,23,34,36,37} as well as in

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Table 1. Studies Examining Insulin Adsorption in Medical Infusion Sets.

	Setting	Line material	Line vol (mL)	Insulin type	Input conc (U/mL)
Fuloria et al ⁶	NICU	PE, PVC	0.3 and 1	Novolin R	0.2
Hewson et al ⁷	NICU	PVC	4	Actrapid	0.2
Jakobsson et al ⁸	ICU	PE	1.6	Neutral	1
Masse et al ¹³	General ICU	PE, PVC, PE/PVC	1 ^a	Humulin R, ^b NovoRapid	1
Zahid et al ¹⁰	ICU/NICU	PE/PVC	1.6, 0.4	Actrapid	1

Abbreviations: PE, polyethylene; PVC, polyvinyl chloride.

^aData in Masse et al appears to have been derived from a variety of different lines and normalized to a 1 mL priming volume.

^bMasse et al specify Umluline Rapide, a French release.

the presence of silicone,^{9,38} a common syringe lubricant. Thus, insulin adsorbs to a wide range of common clinical materials, so losses can occur at a number of points during infusion delivery.

For insulin, only one attempt by a single group has been made to model insulin adsorption and aggregation,^{31,32} but the resulting model is complex and has little clinical applicability. More broadly, insulin adsorption studies can largely be split by audience into clinical and materials science, with very little crossover. The underlying mechanics of the insulin adsorption process have been well examined at material surfaces and interfaces in a materials science context (eg, Refs 29, 30, 35, 39, 40), providing insight into the mechanisms behind adsorptive processes, but not providing clinical context or guidance.

More broadly, the general protein adsorption model has two main modeling approaches: kinetic and thermodynamic,²⁸ where the latter is outside the scope of this paper. In terms of kinetic models, Langmuir and pseudo-first or pseudo-second order models^{41,42} are commonly used. However, these are typically used to describe equilibrium states, rather than the dynamics of the adsorption processes, which are important for insulin dosing in the first one to six hours^{6-8,10} of care or a new infusion line. In addition, they can be limited by assumptions around rigid body binding, where no denaturing occurs, which is not true of proteins.²⁸ Other protein adsorption modeling approaches are summarized in Ref. 28, with variations in complexity typically reflected in the number of states. Since only insulin in solution is readily measured, a primary limitation of the more complex models is they have too many states to be practically identifiable in a clinical setting.⁴³

Early work on a compartment model describing insulin recovery at the outlet of an infusion line has been able to describe the dynamic changes in the percentage recovery, and thus delivery, of insulin.^{44,45} However, low agreement in terms of parameter values was achieved within materials, which limits predictive capacity for different flow rates and concentrations. In particular, the total amount of insulin not recovered, and thus bound to the infusion line, varies between and within literature studies with similar materials. Other studies have shown the total amount of insulin bound to a

material at equilibrium is dependent on the concentration of the solution used.^{39,40} This study quantifies total insulin adsorption to a material surface and examines its relationship flow rate, hypothesizing that flow rate is an important factor in the adsorptive capacity of a material. This study is a first step toward comprehensive modeling of insulin adsorption for clinical use in the management of this phenomenon.

Methods

Literature Search

A literature search was carried out using PubMed and Google Scholar, with combinations of search terms including “Insulin,” “infusion,” “line,” “set,” “adsorption,” “delivery,” “binding,” “removal.” Search results were filtered to those which reported a time-profile of insulin concentrations from the outlet of an insulin infusion line, given a known input insulin concentration, and relevant line characteristics. The resulting studies are summarized in Table 1. The two common materials used in clinical infusion lines are polyvinyl chloride (PVC) and polyethylene (PE), both of which are represented.

Data extraction (DataThief III, Bas Tummings, 2015) was used to tabulate the percentage recoveries of insulin at the line outlet in plotted data. The values were rounded to the nearest 0.1% and carry a maximum estimated error of $\pm 0.1\%$ from the data extraction process. Masse et al¹³ reported tabulated numbers, so their values do not carry this error. Raw data is plotted for reference in Figure 1 and shows the range of different results across studies.

Adsorption Calculations

Two main calculations were made: (1) calculation of insulin delivery based on the area under the curve (AUC) and (2) calculation of adsorption capacity based on AUC and the line surface area (SA).

Insulin delivery. Insulin delivery is calculated as follows:

$$\text{delivery} = \text{AUC}(T, F \times q) \quad (1)$$

Figure 1. Time-varying concentration of insulin at the line outlet in A: polyethylene (PE), B and C: polyvinyl chloride (PVC) lines. Various studies show steady state at concentrations greater or lower than 100% (1.0 or 0.2 U/mL).

where delivery is in insulin U, F is the outlet concentration of insulin (U/mL), and q is the flow rate (mL/h). AUC was calculated from tabulated discrete data using Matlab's (Matlab R2018b, Mathworks, 2018) *trapz* function. Percent of expected delivery was defined as

$$\% \text{delivery} = \frac{\text{AUC}(T, F \times q \times F_0)}{q \times F_0 \times t} \quad (2)$$

where t is time in hours since the first data point is recorded and F_0 is the input concentration. Studies are split between reporting a data point at time zero⁶ and 15-30 minutes into the experiment.^{7,10,13} In addition, it is not always clear how quickly the line is filled (prefill or at experimental flow), or whether time is taken from the onset of insulin input into the line, or the time at which insulin begins to exit the line. This issue does not affect this analysis, as it just introduces an offset in the timing, which does not affect the AUC calculation.

Material adsorption capacity. The adsorption capacity of the material is estimated from the total insulin not recovered by the time the outlet concentration returns to 100%, and the infusion line's inner SA:

$$B_{\text{eq}} = \frac{\text{AUC}(T, (F_0 - F) \times q)}{S_A} \quad (3)$$

where B_{eq} is the total (equilibrium) insulin "bound" or adsorbed to line material (U/m²) and S_A is the internal SA of the line (m²), which is estimated from the line length and priming volume as most studies do not report the internal radius.

The adsorption capacity calculation in Equation (3) assumes outlet concentration has returned to 100%, and can be skewed by reported concentrations greater than 100% where flow rates are high.^{10,13} While concentrations greater than 100% may be possible in the case of desorption of bound insulin, this behavior seems relatively unlikely⁴⁰ and falls within the maximum insulin assay measurement error of ~5% we have observed using high-performance liquid chromatography (HPLC; results not shown here). As each of the studies had differing methodology and outcomes, a set of assumptions were applied separately to the data before applying the calculation in Equation (3):

1. Setting the maximum concentration at the outlet equal to 100% of the input concentration. The maximum outlet concentration across all studies was 103%.

Table 2. Key Methodological Variables and Adsorption Characteristics of PE Tubing From Literature.

Insulin type	Jakobsson et al	Fuloria et al	Masse et al		Zahid et al		
	Neutral insulin	Novolin R	Humulin R	NovoRapid	Actrapid		
Length (cm)	200	152	100		200		
Priming vol	1.6	1	0.78		1.6		
SA:Vol (m ² :mL)	0.004	0.0044:1	0.0040:1		0.0035:1		
Nominal conc (U/mL)	1	0.2	1		1		
Flow rate (mL/h)	1	0.2	2		0.5	1	4
% delivery 6 h	96.1	^a	100	98.8	94.6	98.6	99.7
% delivery 24 h	96.8	61.9	99	99			
Insulin adsorbed (U/m ²)							
Raw	117.1	83.8	146.4	102.3	28.1	5.4	-6.4
If max return = 100%	117.1	83.8	157.7	102.3	31.9	15.2	13.8
If steady state assumed < nominal conc	13.9	49.8	22.1	87.4	N/A	N/A	N/A
If 100% assumed at 48 h	179.6	100.8	N/A	N/A	N/A	N/A	N/A

Adsorptive capacity is calculated using the trapezium rule under various assumptions on steady state. The mostly likely values are italicized by study based on study methodology.

^a6-hour measurement not available.

- Where all outlet concentrations are <100% in a data set, the input concentration is set equal to either the final value (where no clear steady state has been reached, eg, Refs 6 and 7) or the average of the last three data points (where a steady state seems apparent, eg, Refs 8 and 13).
- Where all outlet concentrations are <100% in a data set (eg, Ref 6), the outlet concentration is set to 100% at 48 hours.

The first assumption considers the case where adsorption capacity calculations may return a result that is too low, as faster flow rates combined with insulin concentrations >100% at steady state over a number of hours (as in Zahid et al¹⁰) can cause significant apparent insulin “return” in calculation. This assumption provides a conservative case for maximum adsorption, where measurement errors or insulin losses in the syringe provide a >100% skew.

Assumptions 2 and 3 allow data which has not reached 100% to provide an estimate for capacity. In cases where the methods clearly state that input concentration is directly measured,^{6,10,13} as opposed to an assumption of nominal concentration, assumption 3 is likely more valid than assumption 2 in the case of final insulin outlet concentrations more than 3%-5% lower than the expected 100%.

All assumptions are applied to relevant data sets, and the most likely outcome based on careful analysis of the methodology and plotted results is selected. Where concentrations exceeded 100%, assumption 1 was considered most appropriate. Where steady state concentrations were less than 100% and no mention in the methodology was made of measuring the insulin concentration of the stock/syringe solution, assumption 2 was made. Where the stock/syringe solution insulin concentration was measured and final concentrations

were <100%, assumption 3 was made. Figure 1 plots the raw time-dependent outlet concentrations of insulin to support the assumptions made from the data and show the range of different results across studies. Results from adsorption capacity under all assumptions are given for clarity and completeness.

Analysis

Adsorption capacity results are separated by material type, insulin type, and in some cases insulin concentration, as these are the other major variables expected to affect adsorption capacity. Hyperbolic trend lines, chosen to reflect data outcomes, are fit to data using Matlab’s plot fitting toolbox, and the R^2 value reported. No statistical analysis is carried out due to limited data and data limitations. Such statistical analysis can be found in the original papers, where experimental ranges or standard deviations supplement the plotted data averages.

Relationships between adsorptive capacity and flow rate are used to simulate estimates for insulin adsorptive losses at typical ICU and NICU rates and concentrations. For the purposes of this exercise it is assumed that all insulin loss occurs within 24 hours, which may not be true at very low flow rates and concentrations. This analysis provides clinical context and demonstrates the value of model-based approaches when accounting for adsorptive losses in insulin dosing.

Results

Polyethylene

Table 2 presents adsorptive capacity results, per Equation (3), for PE. Adsorptive capacity is highly dependent on the assumptions applied to the data processing. All

Figure 2. Adsorptive capacity as a function of flow rate for human insulins and A: polyethylene (PE), B: polyvinyl chloride (PVC) lines. Subplots C and D replot the data in A and B for the inverse of flow. Values are taken from those italicized in Tables 2 and 3. *The line of best fit excludes the Fuloria et al data point shown at 0.05 mL/h.

assumptions are applied to all data for consistency, but the most likely results based on study methodology are highlighted in Table 2, as per the assumption elimination criteria in the section “Adsorption Calculations.” Figure 2(a) shows adsorptive capacity decreases hyperbolically to a nonzero minimum value ($R^2 = 0.94$). This trend still holds only if the Zahid et al data are analyzed ($R^2 = 0.82$), an internally consistent result. It should be noted that the steep hyperbolic decay slope can result in low R^2 values for data that is horizontally similar, as reflected in the $R^2 = 0.36$ value for the Zahid trend line evaluated against all the data.

The adsorption capacity of the PE infusion sets estimated solely from raw data ranges from 5 to 146 U/m², compared to the more likely range of 5–100 U/m² based on the applied assumptions in Table 2. The data from Zahid et al¹⁰ returned concentrations of the order 100%–103%, which in this analysis can make raw data estimates of adsorptive capacity lower than what is likely true, where these >100% concentrations are assumed measurement error rather than a desorptive

return of insulin. The 4-mL/h data from Zahid et al¹⁰ demonstrates the rationale for this assumption, where desorption would return more insulin than was actually adsorbed, resulting in an impossible negative adsorptive capacity. The 4-mL/h flow rate also demonstrates the measurement error magnification, similar to the Masse et al PVC results in Table 2.

Polyvinyl Chloride

Insulin adsorption capacities for PVC typically range from 16 to 50 U/m² after assumption application and are presented in Table 3 and Figure 2(b), with time dynamics shown in Figure 1. Estimates of this adsorption capacity, for the most part, assume a return to 100% by 48 hours, excepting the Masse et al data, which at a flow rate of 2 mL/h reached steady state early in the experiment.¹³ Within the Masse et al data, insulin NovoRapid recovery maintained a steady state at 98%–99% for close to 20 hours, so a slightly lower input concentration than nominally intended is a reasonable assumption.

Table 3. Key Methodological Variables and Adsorption Characteristics of PVC Tubing From Literature.

Insulin type	Hewson et al ⁷		Fuloria et al ⁶		Masse et al ¹³		Zahid et al ¹⁰	
	Actrapid		Novolin R		Humulin R	NovoRapid	Actrapid	
Length (cm)	203		152		100		150	
Priming vol	4		0.3		0.78		0.4	
SA:Vol (m ² :mL)	0.0025:1		0.008:1		0.0040:1		0.0059:1	
Nominal conc (U/mL)	0.2	0.2	0.2	0.2	1		1	1
Flow rate (mL/h)	1	0.5	0.2	0.05	2		0.5	0.1
% delivery 6 h (reported)	44.1 (43.9)	26.7 (26.7)	^a	^a	98.6	97.6	72.7	62.5
% delivery 24 h	59.8 ^b	47.6 ^b	68.7	51.7	98.8	97.9	83.5	76.6
Insulin adsorbed (U/m ²)								
Raw	17.6	11.4	125.7	48.4	45.83 ^c	311.5	842.5	237.8
If steady state assumed < nominal conc	4.4	3.3	65.6	43.4	N/A	37.7 ^d	358.6	135.9
If 100% assumed at 48 h	25.3	16.1	157.4	50.9	N/A	N/A	1046.2	288.7

Adsorptive capacity is calculated using the trapezium rule under various assumptions on steady state. The mostly likely values are italicized by study based on study methodology. Actrapid, Novolin R, and Humulin are all human recombinant insulins. NovoRapid is a faster acting insulin analog by comparison.

^a6-hour measurement not available.

^b22 hours.

^cUsing data points up until the first >100% measurement.

^dEstimating steady state as 98.5%, the average of the last few data points.

In general, for each individual experiment the adsorption capacity is higher at the higher flow rate. Despite this, there is an overall trend for lower adsorptive capacity with higher flow rate, as shown in Figure 2(b). As in the PE data, the overall trend in adsorptive capacity decreases hyperbolically to a nonzero minimum value ($R^2 = 0.95$). Adsorption is generally higher in PVC than in PE lines, which is not unexpected.³⁶

Figure 2(b) does not show the Zahid et al data point at 0.5 mL/h in Table 3, as its adsorptive capacity seems extraordinarily high relative to other studies. The line of best fit also excludes the Fuloria et al data point at 0.05 mL/h, where including that point drops the R^2 value to 0.07 due to the steepness of the hyperbolic drop. The extremely low mass flow rate (0.01 U/h) associated with this 0.05 mL/h flow rate may impact to full insulin recovery or affect adsorption dynamics, and a dearth of data at these extremely low mass flow rates means further experimental data is required as part of future work.

Model-Based Clinical Insulin Deliveries

The lines of best fit from Figure 2(a) and (b) are used to estimate total adsorption at different flow rates, concentrations, and SA to volume ratios (SA:V). The total insulin losses in Table 4 broadly match the percentage losses in Tables 2 and 3, as expected. As flow rate and concentration increase, the total adsorptive insulin loss is lower and represents a lower fraction of total delivery, thus reducing the overall impact on 24-hour delivery. In contrast, where flow rates and concentrations are lower, the adsorptive capacity increases and this total loss represents a much greater fraction of total loss. Thus, in low flow, low concentration situations, 24-hour

insulin delivery may be as low as 30%-60% of intended delivery, which likely has significant implications for care.

Discussion

Results and Implications

Adsorption capacity for two common materials (PE, PVC) was calculated from literature data and found to be a function of flow rate, where at higher flow rates the total insulin adsorbed per square meter appears to drop to some lower limit or plateau. This result was observed in data collated from five independent studies with two different materials and multiple flow rates and concentrations. This broad trend warrants further investigation from a single, more complete, study across multiple flow rates, as such conformity would enable its clinical application in setting up infusions.

This study presents a first-ever suggestion that the total amount of insulin lost to adsorption in a hospital line will vary depending on the flow rate used. This study does not directly examine the time course of this loss, which occurs predominantly early in the infusion and decreases over time. However, it adds to the growing body of evidence suggesting insulin adsorption is a function of material, SA, insulin concentration, flow rate, and temperature.

The hyperbolic relationship between insulin adsorptive capacity and flow rate was chosen as an empirical description of the data trend, and not intended to specifically imply underlying mechanisms of adsorption. Similar decreasing curves for adsorptive capacity (also called binding capacity) and flow rate have been noted in other protein adsorption contexts,^{46,47} though not all these curves are likely specifically fit by a hyperbolic trend. In the case of the current study, simple

Table 4. Estimated Adsorptive Capacities and Their Implications for 24-hour Insulin Delivery. Results for the ICU/NICU/PICU are reported as % actual vs. expected delivery of insulin at the flow rates examined.

PE		ICU			More typical of NICU/PICU						
Flow rate	B_{eq} (U/m ²)	Insulin adsorbed in a 1-mL line (U)			24 U in 24 h (avg 1 U/h)	2.4 U in 24 h (avg 0.1 U/h)			1.2 U in 24 h (avg 0.05 U/h)		
		SA:V 0.004:1	SA:V 0.006:1	SA:V 0.008:1	SA:V 0.004:1	SA:V 0.004:1	SA:V 0.006:1	SA:V 0.008:1	SA:V 0.004:1	SA:V 0.006:1	SA:V 0.008:1
0.2	96.5	0.4	0.6	0.8	98.4	83.9	75.9	67.8	67.8	51.8	35.7
0.5	40.1	0.2	0.2	0.3	99.3	93.3	90.0	86.6	86.6	80.0	73.3
1	21.3	0.1	0.1	0.2	99.6	96.5	94.7	92.9	92.9	89.4	85.8
2	11.9	0.0	0.1	0.1	99.8	98.0	97.0	96.0	96.0	94.1	92.1

PVC		ICU			More typical of NICU/PICU						
Flow rate	B_{eq} (U/m ²)	Insulin adsorbed in a 1-mL line (U)			24 U in 24 h (avg 1 U/h)	2.4 U in 24 h (avg 0.1 U/h)			1.2 U in 24 h (avg 0.05 U/h)		
		SA:V 0.004:1	SA:V 0.006:1	SA:V 0.008:1	SA:V 0.004:1	SA:V 0.004:1	SA:V 0.006:1	SA:V 0.008:1	SA:V 0.004:1	SA:V 0.006:1	SA:V 0.008:1
0.2	144.02	0.6	0.9	1.2	97.6	76.0	64.0	52.0	52.0	28.0	4.0
0.5	57.62	0.2	0.3	0.5	99.0	90.4	85.6	80.8	80.8	71.2	61.6
1	28.82	0.1	0.2	0.2	99.5	95.2	92.8	90.4	90.4	85.6	80.8
2	14.42	0.1	0.1	0.1	99.8	97.6	96.4	95.2	95.2	92.8	90.4

Adsorptive capacities are estimated using the trend lines in Figure 2 for PE and PVC, respectively, and it is assumed here that all adsorption occurs within 24 hours.

trends were examined, where linear and parabolic trend lines did not describe the data well, and an exponential trend was unable to capture the steepness of the drop. Future work establishing a single data adsorption and flow variation data set should examine the nature of the adsorptive capacity and flow relationship, as well as try to relate it to fundamental chemistry and fluid dynamics relationships if possible.

A hyperbolic-type relationship between adsorptive capacity and flow rate was clearer in the PE lines than the PVC. In particular, several studies with two flow rates^{6,7,10} show a higher adsorption capacity at the higher flow. This is intriguing, but data limitations make such trends uncertain. Hewson et al⁷ prefilled the infusion line to remove air bubbles, sometimes resulting in uncollected insulin output at the end of the line prior to infusion initiation.⁷ This will likely impact the relative insulin recovery at the two flow rates used. One result from Zahid et al¹⁰ was extremely high relative to all other results (Table 3), which requires further investigation. Further, some PVC lines were plasticized,^{7,13} which affects adsorption,¹³ and lines differ significantly in SA to volume ratios (Table 3), compared to PE (Table 2).

A further consideration comparing results between PVC and PE is that the PE data was mostly at concentrations of 1.0 U/mL, whereas that for PVC was a mix of 0.2 and 1.0 U/mL. The lowest mass flow rate for insulin as 0.01 U/h under flow conditions of 0.05 mL/h and 0.2 U/mL, compared to a

majority of the remainder of flow rates greater than 0.1 U/h. At very low flow mass rates it is entirely possible that other adsorption dynamics with much slower time constants come into play. For example, the subsequent, usually slow,²⁸ denaturing of proteins on a sparsely bound surface often results in greater SA footprints per molecule.²⁸ In faster flow, more rapid binding of insulin due to rapid presentation at binding sites adjusts the energy balance for both surface and insulin-insulin binding and can change the orientation and packing of proteins at the surface²⁸ and may reduce conformational changes. Alternatively, radial diffusion within pipe flow may also play more of a role at low concentrations. Future work should examine dynamics at low mass flow rate conditions under consistent methodological conditions.

The study by Masse et al also suggests insulin type may affect results, as shown in Tables 2 and 3. The different rapid-acting insulins are similar to regular human insulin, but with an amino acid interchange or switch at a particular position in their chains.⁴⁸ Thus, these results begin to provide much needed insight into the factors significantly affecting clinical insulin delivery.

Comparison to literature. Insulin adsorption to surfaces and interfaces has been well examined in the laboratory context, typically using beads and much higher concentrations of insulin than used clinically. The insulin adsorption capacity

Figure 3. Total insulin adsorbed to Teflon surfaces (without rinsing) at equilibrium at various insulin bulk solution concentrations. Results are adapted from Mollmann et al,^{39,40} only including results at pH 7.4. (a) Adsorbed insulin over 0-30 U/mL. (b) Detail of range 0-1.0 U/mL.

of Teflon in particular has been studied.^{39,40} Equilibrium concentrations of insulin on the material surface were measured at different bulk fluid insulin concentrations, where a rapid increase in the total insulin bound to a plateau at concentrations greater than 0.2-0.5 U/mL demonstrated the high binding affinity of insulin to hydrophobic Teflon surfaces,^{39,40} shown in Figure 3. Adsorption on this surface also changes the insulin structure.²⁹ Lower surface concentrations at lower bulk solution concentrations were attributed to insulin deformation on the surface and greater distances between molecules, and slower time to equilibrium suggests limitations due to bulk solution diffusion rates.³⁹ Re-evaluation of the surface concentration after rinsing showed lower bound insulin concentrations, suggesting a second layer of insulin³⁰ not directly bound to the hydrophobic surface can be desorbed.³⁹ In this case, surface concentrations of adsorbed insulin suggested a mix of monomers and dimers.³⁹

During flow, diffusion processes are likely negligible, and the adsorption capacity is likely limited by either mechanical shear at the solid-liquid interface, which may limit the number of layers, or the relative time constant difference between adsorptive binding and insulin denaturing. In Mollman et al³⁹ adsorption capacities are calculated around 78 U/m² (2.7 mg/m²), which are most likely hexameric in nature if a single layer of adsorption is assumed, compared to 32-63 U/m² (1.1-2.2 mg/m²) for monomeric or dimeric packing.³⁹ In the case of low flows, the results in Figure 2 are sometimes higher than this latter value, suggesting several layers of adsorption, a result supported by experiments in adsorption kinetics.^{30,35}

In Figure 2 the surface adsorptions calculated under higher flow conditions compare well to theoretical values for a single mixed monomeric and dimeric adsorbed layer (32-63 U/m²). It is unclear whether some equilibrium exchange

between bound and unbound insulin occurs.^{30,40} Though Mollman et al^{39,40} only consider Teflon, their results should be broadly translatable, at least in trend, to PE and PVC, as they are also hydrophobic material.

Another study examining a flat hydrophobic surface exposed to flow found adsorbed insulin bound more strongly to the surface after more than 1 hour of contact, and insulin aggregates may form on the preliminary surface insulin layer.³⁰ These aggregates form on hydrophobic beads with ~230 U/m² (8 mg/m²) of insulin deposition,³³ a result much higher than most of the adsorptions in Tables 2 and 3. Thus, it seems unlikely that large aggregates are forming under the clinical conditions studied here.

Clinical implications. These adsorption capacity results have strong implications clinically, particularly in the instance where flow rates are slower than 1 mL/h, as shown in Table 4. A direct implication is that the amount of insulin adsorbed, and therefore not delivered, will approximately double for flow rates at 0.5 mL/h compared to 1 mL/h, or quadruple for flow rates of 0.2 mL/h compared to 1 mL/h. Thus, estimations at the bedside of percentage loss are not trivial, depending on a number of factors, a result reflected in the lack of progress in this area from the late 1960s.

The impact of these results varies depending on context. In the adult ICU, where the concentration is more typically 1.0 U/mL, and flow rates are usually higher than 1 mL/h, only the first hour or two of delivery might be significantly affected, and the fraction of 24-hour insulin delivery is likely to be approximately 98% or higher. In this case, low insulin sensitivity might be erroneously observed early in insulin therapy, which normalizes within one to six hours. Unintended hypoglycemia is also a possibility in this early infusion period, where apparent insulin resistance caused by

undelivered insulin results in higher than optimal insulin doses.

In low flow and low dose situations, the fraction of 24-hour insulin delivery can range between 50% and 80%, depending on the line used and the total 24-hour dosage. Thus, insulin therapy in NICU and PICUs is likely more directly affected by this issue.^{6,7} However, higher insulin infusion has been noted in the adult ICU when infusion sets are changed,⁸ or between PE and polyurethane lines,³⁶ indicating a noticeable effect.

Priming or flushing can significantly reduce the effect of adsorption on clinical delivery of insulin.^{6,7} Essentially flushing the infusion line with insulin, with or without a soaking period, allows insulin to bind to the material surface, reducing available binding sites during therapeutic insulin delivery. The preconditioning or flushes examined in Refs 6 and 7 involved much higher concentrations of insulin (5 vs 0.2 U/mL)⁶ or large flush volumes (20-50 mL) and/or soak times (up to one hour).^{7,11} These practices may be clinically infeasible from a resource or workload perspective. However, the recommendation for preflushing, even if only to replace one to two priming volumes, is of potentially significant value in reducing undelivered insulin and should be considered in all low flow and low concentration therapies.

Modeling implications. There is a need for quantitative estimations of adsorptive loss of insulin in hospital lines across a range of materials, insulin concentrations, and flow rates. Model-based methods are well placed to generalize material properties for the prediction of adsorptive losses at any combination of concentration and flow rate. Early analysis of compartment-based models has shown promise,^{44,45} but lacked generalization of model parameters within a material. This study adds significant cohesiveness to these previously noted disparities^{44,45} and provides an important method for predicting the total adsorptive capacity (B_{eq}) available. Future work should examine the interaction of this total capacity with the time dynamics of loss. There is also a need to consider how adsorptive capacity is affected by more frequent changes in flow rate, as found in any clinical delivery setting.

Quantification of adsorptive loss and its time variance have important implications for dosing and model-based metrics of insulin sensitivity.⁴⁹⁻⁵¹ Insulin sensitivity may inaccurately appear low in initial hours, due to undelivered insulin being adsorbed to the line surface. This issue could result in persistent early hyperglycemia or later overdosing of insulin and hypoglycemia when apparent resistance is treated within an increased insulin dose. Fuloria et al⁶ noted persistent hyperglycemia in the first few hours of an insulin infusion, and Jakobsson et al⁸ have noted higher insulin dosing in the first few hours of an insulin infusion with a new line. Thus, adsorption has implications for clinical settings that may be accounted for using model-based methods.⁴⁵

Limitations

A number of assumptions were applied to the data, based on recorded methodology from the original paper, as described in the section “Adsorption Calculations”. The application of these assumptions, combined with data from several different sources with different methodologies and measurement techniques, is a limitation in this study, and future work should examine the effect of flow rate on adsorption capacity in a single comprehensive study.

One assumption set the maximum insulin in solution concentration at the line output to 100%. Our own (unpublished) experience with HPLC, the predominant measurement methodology across these research studies, suggests 1%-5% variation in samples taken from the same bulk solution depending on time delay to HPLC measurement (0-12 hours) and exposure to primed/unprimed pipette tips during sampling. For a series of measures taken and analyzed immediately, a 0.5%-1% variation was observed. Thus, where data seem to reach steady states close to or above 100% it seems reasonable to assume the outlet concentration has reached the input concentration and no further adsorption is occurring. This can result in higher insulin return than theoretically present in the system, as was demonstrated in the Zahid et al 4-mL/h data resulting in an adsorptive capacity of -6.4 U/m^2 (Table 2). Constant outlet concentrations of insulin solution greater than 100% suggest a constant source or stripping of insulin previously bound to the hydrophobic material surface, which seems unlikely in the presence of continuous insulin flow.⁴⁰ Future studies should consider sampling outlet reservoir concentrations for total insulin return, as per,¹⁴ in addition to the outlet samples for adsorption dynamics.

Another assumption set the input concentration equal to the final outlet concentration, where steady state less than 100% was achieved. These assumptions are reasonable based on both measurement error, and known losses to syringes ($\sim 2\%$)¹⁰ and glass (beaker) surfaces.^{34,35,52} In the latter case, losses in vials,⁵³ mixing surfaces, or syringes would result in a bulk solution concentration lower than the nominal expected concentration. Several studies^{6,10,13} accounted for this loss with bulk solution measurement(s), while the remaining studies do not appear to manage this issue. This assumption is then best applied in the latter set of studies.

The data from Masse et al¹³ demonstrates the importance of flow rates when considering total adsorption. Higher flow rates at high concentrations may amplify measurement error or input uncertainty with regard to the steady state, significantly affecting AUC as demonstrated in the 311.5 vs 37.7 U/m² adsorption capacity values. This follows from Equations (1) and (2), where AUC and adsorptive capacity are directly functions of flow rate. At higher flow rates, dynamics are also faster, and the percent recovery values at the outlet reach 100% over much shorter time periods, so important dynamics may be missed if only higher flow rates are considered. Flow rates of 0.5 or 1

mL/h seem to provide good resolution of adsorption dynamics at concentrations of 1.0 U/h.

Error during data extraction may add $\pm 0.1\%$ error to output insulin concentrations. This error is based on graph resolution and, where relevant, uncertainty on the center point of data squares/triangles/circles. The possible exception is Hewson et al,⁷ whose graphical grid resolution was lower on the *Y*-axis than other studies. Masse et al¹³ reported tabulated numbers. In the cases where error bars are provided, the $\pm 0.1\%$ estimation error was much lower than the error bars. Thus graphical data extraction is not expected to significantly impact results.

Measurement methodology between studies differed. Several studies^{8,10,13} used HPLC, while the remaining used radioimmunoassays.^{6,7} In particular, the insulin concentration from Zahid et al¹⁰ and Jakobsson et al⁸ may also include any preservatives in the insulin solution due to the wavelengths used in HPLC.¹³ These preservatives are not necessarily factored out by dividing through by the original concentration, as Zahid et al did, as preservatives can also adsorb.¹³ However, the data point by Masse et al¹³ in Figure 2(a) is higher than those from Zahid et al and Jakobsson et al, suggesting this effect may not be significant. The overall trend lines in Figure 2 still seem to hold, particularly as Zahid et al is internally consistent in Figure 2(a).

Each of the studies also had their inherent limitations. One of the most significant was the lack of clarity around whether time $t = 0$ corresponded to the onset of infusion at the line inlet or the collection of the first few drops of solution at the line outlet. It is not always clear whether the $t = 0$ sample represents the concentration of the stock solution at the inlet or the first few drops of insulin to exit the line. This issue does not affect this analysis, as it just introduces an offset in the timing which does not affect the AUC calculation. In addition, some of the studies, namely Zahid et al¹⁰ and Masse et al,¹³ took their first sample at $t = 30$ minutes. In Masse et al, time is measured from infusion onset at the inlet, and so, depending on the line length, 30 minutes might be close to the egress of the first fluid (within 7 minutes for their 1 mm diameter, 1 m length line to which the data is normalized). Masse et al also present their results from many different line lengths and diameters as a single scaled or adapted data set per material,¹³ which may affect early reporting of dynamics. In the case of these two studies, the insulin adsorption capacity is likely to be slightly higher than calculated due to the loss of the first 7-30 minutes of data. This error is unlikely to significantly raise the calculated adsorption capacity and will not affect the overall observed hyperbolic trend.

Though less important in this study, the flow rate at which the line was filled also has significant implications for study of the dynamics of adsorption. In Jakobsson et al⁸ and Zahid et al¹⁰ at $t = 0$ plotted recovery of insulin starts at 100%. Given other studies^{6,7} report the first sample collected at the line outlet has concentration less than 100%, it seems likely

this 100% at $t = 0$ is the concentration of the stock solution, rather than outlet sample, particularly since Zahid et al¹⁰ report their first sample at 30 minutes in their methods. While in this study only the total insulin adsorbed is calculated, for future work examining the dynamics of these losses the value of that first sample, which can be considered as a kind of “initial condition,” is vitally important for model parameter identification. Future work will require a comprehensive data set collected under clear flow conditions for model identification validation. The discrepancies and lack of clarity across the range of studies collected are a good reminder about “blind spots” in experimental practice and the importance of reproducible methodologies.

Future Work

This study is a first step toward a twofold goal of using models to better understand the dynamics of clinical insulin adsorption and utilization of these models and knowledge to improve the precision of insulin dosing. There is a scarcity of literature in the area of clinical applications to elucidate the dynamics of adsorption over a wide range of common clinical contexts and applications. Validated model-based methods have the advantage of exploring a wide range of clinical concentrations, flow rates, and line geometries at a fraction of the time, effort, and experimental cost. Models developed for insulin are also likely extendable to other protein-based therapeutics.

Model-based methods can also improve the precision of diagnostic model-based measures of insulin sensitivity and insulin dosing. At the bedside, they may be used to directly account for or compensate for insulin loss during delivery, where future work will need to consider the effect of changes in flow rate over the course of therapy. In addition, these models could be used to design priming or delivery protocols. In the former case, such a priming protocol would optimize presaturation of insulin binding sites for minimum wastage or clinical workload and delay in therapy onset. Insights into insulin adsorption dynamics could also lead to optimization of the delivery parameters (flow rate and how this rate changes over time, concentration, material, line geometry) for insulin therapy. In summary, the current work provides useful insights into one aspect of insulin adsorption, namely total binding capacity, and is a step toward an end model with potentially significant implications for protein therapeutics.

Conclusions

PE and PVC infusion lines are commonly used to deliver insulin. Insulin adsorption to these lines is well documented, but not well quantified. The total capacity of a material for insulin adsorption (U/m²) was found to be nonconstant, and had a hyperbolic-shaped relationship with flow. This result was true for both PE and PVC, where in low flow insulin

infusions the adsorption capacity of the line doubled when the infusion flow rate was halved from 1 to 0.5 mL/h. This increased capacity at low flow could be explained by reduced shear allowing more insulin layers to deposit. Thus, adsorption capacity changes with flow have significant implications for low flow and low concentration infusions, such as might be delivered in neonatal or pediatric intensive care, where total adsorption often represents 30%-60% of total insulin delivery over 24 hours. Overall, the results presented here provide a first cohesive explanation for disparities in existing literature and can be used in a modeling framework to describe, predict, and directly account for clinical insulin adsorption.

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References

- Weisenfeld S, Podolsky S, Goldsmith L, Ziff L. Adsorption of insulin to infusion bottles and tubing. *Diabetes*. 1968;17(12):766-771.
- Schildt B, Ahlgren T, Berghem L, Wendt Y. Adsorption of insulin by infusion materials. *Acta Anaesthesiol Scand*. 1978;22(5):556-562.
- Peterson L, Caldwell J, Hoffman J. Insulin adsorbance to polyvinylchloride surfaces with implications for constant-infusion therapy. *Diabetes*. 1976;25(1):72-74.
- Twardowski ZJ, Nolph KD, McGary TJ, Moore HL. Influence of temperature and time on insulin adsorption to plastic bags. *Am J Hosp Pharm*. 1983;40(4):583-586.
- Sato S, Ebert CD, Kim SW. Prevention of insulin self-association and surface adsorption. *J Pharm Sci*. 1983;72(3):228-232.
- Fuloria M, Friedberg MA, DuRant RH, Aschner JL. Effect of flow rate and insulin priming on the recovery of insulin from microbore infusion tubing. *Pediatrics*. 1998;102(6):1401-1406.
- Hewson M, Nawadra V, Oliver J, Odgers C, Plummer J, Simmer K. Insulin infusions in the neonatal unit: delivery variation due to adsorption. *J Paed Child Health*. 2000;36(3):216-220.
- Jakobsson T, Shulman R, Gill H, Taylor K. The impact of insulin adsorption onto the infusion sets in the adult intensive care unit. *J Diabetes Sci Technol*. 2009;3(1):213-214. doi:10.1177/1932296809000300126
- Nayef L, Khan MF, Brook MA. The stability of insulin solutions in syringes is improved by ensuring lower molecular weight silicone lubricants are absent. *Heliyon*. 2017;3(3):e00264. doi:10.1016/j.heliyon.2017.e00264
- Zahid N, Taylor KM, Gill H, Maguire F, Shulman R. Adsorption of insulin onto infusion sets used in adult intensive care unit and neonatal care settings. *Diabetes Res Clin Pract*. 2008;80(3):e11-e13.
- Thompson CD, Vital-Carona J, Faustino EV. The effect of tubing dwell time on insulin adsorption during intravenous insulin infusions. *Diabetes Technol Ther*. 2012;14(10):912-916. doi:10.1089/dia.2012.0098
- Yu KH, Tsao HL, Lin SJ, Chen CY. Quantitative analysis of insulin in total parenteral nutrition bag in Taiwan. *J Food Drug Anal*. 2016;24(1):214-219. doi:10.1016/j.jfda.2015.08.003
- Masse M, Maton M, Genay S, et al. In vitro assessment of the influence of intravenous extension set materials on insulin aspart drug delivery. *PLoS One*. 2018;13(8):e0201623. doi:10.1371/journal.pone.0201623
- Simeon PS, Geffner ME, Levin SR, Lindsey AM. Continuous insulin infusions in neonates: pharmacologic availability of insulin in intravenous solutions. *J Pediatr*. 1994;124(5 Pt 1):818-820.
- Bagshaw S, Bellomo R, Jacka M, et al. The impact of early hypoglycemia and blood glucose variability on outcome in critical illness. *Crit Care*. 2009;13(3):R91.
- Egi M, Bellomo R, Stachowski E, et al. Hypoglycemia and outcome in critically ill patients. *Mayo Clin Proc*. 2010;85(3):217-224. doi:10.4065/mcp.2009.0394
- Finfer S, Liu B, Chittock DR, et al. Hypoglycemia and risk of death in critically ill patients. *N Engl J Med*. 2012;367(12):1108-1118. doi:10.1056/NEJMoa1204942
- Egi M, Bellomo R, Stachowski E, et al. Variability of blood glucose concentration and short-term mortality in critically ill patients. *Anesthesiology*. 2006;105(2):244-252.
- Ali NA, O'Brien JM, Jr., Dungan K, et al. Glucose variability and mortality in patients with sepsis. *Crit Care Med*. 2008;36(8):2316-2321. doi:10.1097/CCM.0b013e3181810378
- Krinsley JS. Glycemic variability: a strong independent predictor of mortality in critically ill patients. *Crit Care Med*. 2008;36(11):3008-3013.
- Pickup JC, Yemane N, Brackenridge A, Pender S. Nonmetabolic complications of continuous subcutaneous insulin infusion: a patient survey. *Diabetes Technol Ther*. 2014;16(3):145-149.
- Klonoff DC, Freckmann G, Heinemann L. Insulin pump occlusions: for patients who have been around the (Infusion) block. *J Diabetes Sci Technol*. 2017;11(3):451-454. doi:10.1177/1932296817700545
- Chawla AS, Hinberg I, Blais P, Johnson D. Aggregation of insulin, containing surfactants, in contact with different materials. *Diabetes*. 1985;34(5):420-424. doi:10.2337/diab.34.5.420
- Tzannis ST, Hrushesky WJM, Wood PA, et al. Adsorption of a formulated protein on a drug delivery device surface. *J Colloid Interface Sci*. 1997;189(2):216-228. doi:10.1006/jcis.1997.4841
- Illum L, Bundgaard H. Sorption of drugs by plastic infusion bags. *Int J Pharm*. 1982;10(4):339-351. doi:10.1016/0378-5173(82)90168-5
- Darcy PF. Drug-interactions with medical plastics. *Drug Intell Clin Pharm*. 1983;17(10):726-731.

27. Sherwin CMT, Medlicott NJ, Reith DM, Broadbend RS. Intravenous drug delivery in neonates: lessons learnt. *Arch Dis Child*. 2014;99(6):590-594.
28. Rabe M, Verdes D, Seeger S. Understanding protein adsorption phenomena at solid surfaces. *Adv Colloid Interface Sci*. 2011;162(1-2):87-106.
29. Jorgensen L, Bennedsen P, Hoffmann SV, et al. Adsorption of insulin with varying self-association profiles to a solid Teflon surface—influence on protein structure, fibrillation tendency and thermal stability. *Eur J Pharm Sci*. 2011;42(5):509-516. doi:10.1016/j.ejps.2011.02.007
30. Nault L, Guo P, Jain B, Bréchet Y, Bruckert F, Weidenhaupt M. Human insulin adsorption kinetics, conformational changes and amyloid aggregate formation on hydrophobic surfaces. *Acta Biomater*. 2013;9(2):5070-5089. doi:10.1016/j.actbio.2012.09.025
31. Sluzky V, Klivanov AM, Langer R. Mechanism of insulin aggregation and stabilization in agitated aqueous solutions. *Biotechnol Bioeng*. 1992;40(8):895-903. doi:10.1002/bit.260400805
32. Sluzky V, Tamada JA, Klivanov AM, Langer R. Kinetics of insulin aggregation in aqueous solutions upon agitation in the presence of hydrophobic surfaces. *Proc Natl Acad Sci USA* 1991;88(21):9377-9381.
33. Pandey LM, Le Denmat S, Delabouglise D, Bruckert F, Pattanayek SK, Weidenhaupt M. Surface chemistry at the nanometer scale influences insulin aggregation. *Colloids Surf B Biointerfaces*. 2012;100:69-76. doi:10.1016/j.col-surf.2012.05.022
34. Petty C, Cunningham NL. Insulin adsorption by glass infusion bottles, polyvinylchloride infusion containers, and intravenous tubing. *Anesthesiology*. 1974;40(4):400-404.
35. Sefton MV, Antonacci GM. Adsorption isotherms of insulin onto various materials. *Diabetes*. 1984;33(7):674-680. doi:10.2337/diab.33.7.674
36. Ley S, Ammann J, Herder C, Dickhaus T, Hartmann M, Kindgen-Milles D. Insulin adsorption to catheter materials used for intensive insulin therapy in critically ill patients: polyethylene versus polyurethane—possible cause of variation in glucose control? *Open Crit Care Med J*. 2014;7(1):1-6. doi:10.2174/1874828701407010001
37. Seres DS. Insulin adsorption to parenteral infusion systems: case report and review of the literature. *Nutr Clin Pract*. 1990;5(3):111-117. doi:10.1177/0115426590005003111
38. Jones LS, Kaufmann A, Middaugh CR. Silicone oil induced aggregation of proteins. *J Pharm Sci*. 2005;94(4):918-927. doi:10.1002/jps.20321
39. Mollmann SH, Bukrinsky JT, Frokjaer S, Elofsson U. Adsorption of human insulin and AspB28 insulin on a PTFE-like surface. *J Colloid Interface Sci*. 2005;286(1):28-35. doi:10.1016/j.jcis.2005.01.018
40. Mollmann SH, Jorgensen L, Bukrinsky JT, Elofsson U, Norde W, Frokjaer S. Interfacial adsorption of insulin conformational changes and reversibility of adsorption. *Eur J Pharm Sci*. 2006;27(2-3):194-204. doi:10.1016/j.ejps.2005.09.010
41. Largitte L, Pasquier R. A review of the kinetics adsorption models and their application to the adsorption of lead by an activated carbon. *Chem Eng Res Design*. 2016;109:495-504. doi:10.1016/j.cherd.2016.02.006
42. Simonin JP. On the comparison of pseudo-first order and pseudo-second order rate laws in the modeling of adsorption kinetics. *Chem Eng J*. 2016;300:254-263. doi:10.1016/j.cej.2016.04.079
43. Docherty PD, Chase JG, Lotz TF, Desai T. A graphical method for practical and informative identifiability analyses of physiological models: a case study of insulin kinetics and sensitivity. *Biomed Eng Online*. 2011;10(1):39. doi:10.1186/1475-925X-10-39
44. Hardy AR, Chase JG, Knopp JL. Model based insulin absorption into intravenous infusion sets in adult and neonatal intensive care unit's. *IFAC-PapersOnLine*. 2018;51(27):24-29. doi:10.1016/j.ifacol.2018.11.602
45. Knopp JL, Hardy AR, Vergeer S, et al. Modelling insulin adsorption in intravenous infusion sets in the intensive care unit. *IFAC J Syst Control*. 2019;8:100042. doi:10.1016/j.ifacsc.2019.100042
46. Erturk G, Bereli N, Ramteke PW, Denizli A. Molecularly imprinted supermacroporous cryogels for myoglobin recognition. *Appl Biochem Biotechnol*. 2014;173(5):1250-1262. doi:10.1007/s12010-014-0844-z
47. Hahn R, Deinhofer K, Machold C, Jungbauer A. Hydrophobic interaction chromatography of proteins. II. Binding capacity, recovery and mass transfer properties. *J Chromatogr B Analyt Technol Biomed Life Sci*. 2003;790(1-2):99-114.
48. Fullerton B, Siebenhofer A, Jeitler K, et al. Short-acting insulin analogues versus regular human insulin for adult, non-pregnant persons with type 2 diabetes mellitus. *Cochrane Database Syst Rev (Online)*. 2018;12:CD013228. doi:10.1002/14651858.CD013228
49. Lin J, Lee D, Chase JG, et al. Stochastic modelling of insulin sensitivity and adaptive glycemic control for critical care. *Comput Methods Programs Biomed*. 2008;89(2):141-152.
50. Pretty CG, Le Compte AJ, Chase JG, et al. Variability of insulin sensitivity during the first 4 days of critical illness: implications for tight glycemic control. *Ann Intensive Care*. 2012;2(1):17. doi:10.1186/2110-5820-2-17
51. Pretty CG, Signal M, Fisk L, et al. Impact of sensor and measurement timing errors on model-based insulin sensitivity. *Comput Methods Programs Biomed*. 2013;114(3):e79-86. doi:10.1016/j.cmpb.2013.08.007
52. Hill JB. The adsorption of I131-insulin to glass. *Endocrinology*. 1959;65:515-517. doi:10.1210/endo-65-3-515
53. Carter AW, Heinemann L. Insulin concentration in vials randomly purchased in pharmacies in the United States: considerable loss in the cold supply chain. *J Diabetes Sci Technol*. 2018;12(4):839-841. doi:10.1177/1932296817747292