Sources of Glycemic Variability—What Type of Technology is Needed?

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Abstract

People on insulin therapy are challenged with evaluation of numerous factors affecting the blood glucose in order to select the optimal dose for reaching their glucose target. Following medical recommendations precisely still results in considerable blood glucose unpredictability, often resulting in frustration in the short term due to hypoglycemia and hyperglycemia, and, in the long term, will likely result in complications.

The kinetics of insulin do indeed vary significantly and have become an important focus when developing new insulin analogues and delivery systems; however, numerous of other factors impact glycemic variability. These have different dependences and interactions and are therefore difficult to characterize. Some of the factors are highly dependent and influenced by the type of insulin and devices used in therapy. Development of future therapy products is therefore highly focused on how to minimize glycemic variability.

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Introduction

Glycemic stability is the major issue for people on insulin therapy, especially since studies have shown how lowering variability can reduce long-term complications.[1,2] However, we have learned that following medical recommendations strictly does not guarantee perfect glycemic stability and that strict therapy has a negative effect on convenience.

Numerous factors influence glycemic variability of people on insulin therapy. They are exposed to variability through physiology and through insulin delivery, which increases uncertainty of their insulin level. Glucose meters have limited accuracy. Also, manual estimation of meal carbohydrates is difficult and adds variability, and lifestyle changes and compliance difficulties are major contributors. Although the different variability effects are interacting, for clarity, these have been divided into five independent categories as illustrated at **Figure 1**.

The motivation for writing this paper is the need to illustrate some of the obstacles having influence on glycemic variability and in parallel to describe the direction in which insulin, devices, and therapy are developed in order to facilitate this.

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Abbreviations: (CGM) continuous glucose monitor, (CV) coefficient of variation, (NPH) neutral protamine Hagedorn, (PK) pharmacokinetic

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Corresponding Author: Jonas Kildegaard, Ph.D., Kildegaard Consult, Borups Allé 148 4. th. 2000 Frederiksberg, Denmark; email address *jonas@kildegaardconsult.dk*
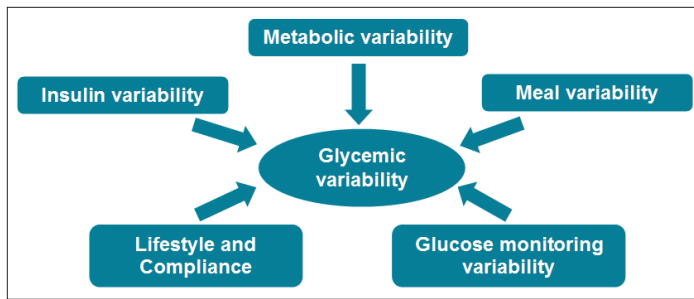
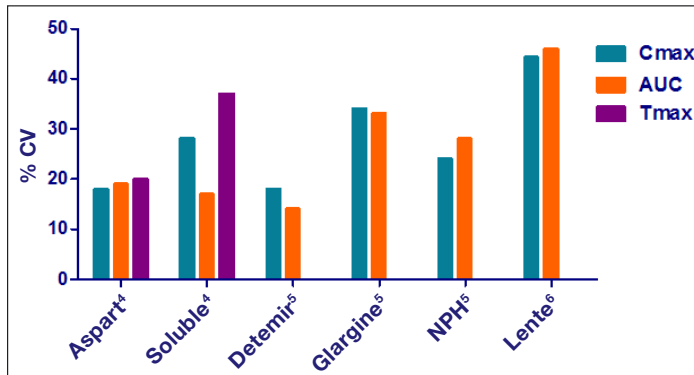Figure 1. Five different factors that influence glycemic variability.

Figure 2. Pharmacokinetic interindividual variability of different insulin preparations.[4–6] Long-acting insulin (detemir, glargine, NPH, and lente) is considered not to have a well-defined peak. Tmax, time of the peak concentration; Cmax, maximal concentration; AUC, area under the curve.

Insulin Variability

With modern insulin and delivery systems, insulin therapy has greatly improved glycemic predictability, and the industry is continuously focusing on improving products in these areas.

Insulin Preparation

Insulin preparations have changed from porcine to human to recombinant insulin. Also, the technology for prolongation of action has changed from crystal insulin preparations to insulin binding to albumin, like detemir.[3] Pharmacokinetic (PK) predictability is important in order to treat as close to glucose target as possible. **Figure 2** shows the PK interindividual variability of different insulin preparations. Intraindividual variability follows the pattern, however, with slightly smaller values. The coefficient of variation (CV) is defined as the ratio of the standard deviation to the mean.

Fast-acting insulin analogues are modified to have a faster rate of diffusion subcutaneously than human insulin. **Figure 2** shows how the traditional crystal insulin,

neutral protamine Hagedorn (NPH), and lente typically introduce more variability than in analogues, illustrated here with Aspart and detemir.[7]

Insulin analogues have been developed primarily to create long-acting basal profiles and fast-acting prandial choices. This trend is likely to continue. Also, the reduced variability has become a key selling point for novel insulin.

Insulin Delivery

Insulin pens have been shown to be more accurate than syringes, with a % CV around 2 compared to around 5 for syringes when delivering 5 U of insulin.[8,9] However, insulin pens still have limited accuracy. When investigating delivery at 5, 10, and 30 IU, the standard deviation of the mean dose delivered by FlexPen were 0.19, 0.27, and 0.34, respectively, and were 0.30, 0.52, and 0.47, respectively, for SoloStar.[10]

Insulin pumps have demonstrated several treatment advances, as it is a flexible platform for tailoring personalized insulin profiles.[11] Pumps are still considered expensive for the majority;[11] however, the number of commercially available insulin pumps is growing, and focus exists on providing less expensive options in the future.

The exact use of the delivery system is another issue, with depth, anatomical site, and delay before withdrawing the needle giving rise to poor reproducibility.[4,12] Time delay before withdrawing the needle causes loss of insulin. In one study,[13] rapid withdrawal of the needle was investigated and led to loss of insulin in 25% of the patients. In 13.8% of the patients, the loss of insulin was 10% of the dose. Also, accidental intramuscular injections of NPH have shown to reduce T50 from 10.3 to 5.3 h.[4,14] Therefore, there are many obstacles to avoid by following therapy guidelines, and simply using the insulin delivery method correctly can improve therapy outcome. These problems are another reason for switching patients to pumps in the future because of the reduced variability that exist between injection boli. Pump therapy eliminates some of the variability factors from injection, although shorter PK peak and duration of action have been observed from insulin catheter aging.[15]

Metabolic Variability

A number of internal factors influence glucose metabolism. Fluctuations in insulin sensitivity and insulin action have been known to be important, considerable contributions to glycemic variability.[16,17] Variability of insulin sensitivity

under clinical conditions have shown an average interday CV of 20.2 +/- 3.2%.[18]

Also, hypoglycemia triggers counter-regulatory mechanisms that give rise to insulin resistance.[19] Hypoglycemia is a complex therapy area regarding rules and is considered, by some, the largest contributor to glycemic variability.[20]

Tissue sensitivity to insulin is affected by outside conditions, for instance, accelerated blood flow as a result of exercise.[21] Although the concept of some of these effects is simple, the consequences in the short term are unpredictable for most people, because it involves dynamic effect of multiple hormones. For example, minor differences in exercise have shown significant changes in blood glucose dynamics.[22,23]

Some of the metabolic fluctuations are known to follow daily patterns.[24] For instance, a significant decrease of insulin sensitivity the luteal phase of the normal menstrual cycle has been observed.[25] Diurnal variation in glycemia and insulin sensitivity have been observed; however, this is still poorly understood.[26] People on insulin therapy are usually aware of the daily patterns, and novel insulin pumps have options to set different insulin gain factors throughout the day. Hence there is a need for technology-assisted retrospective analysis in order to identify these daily fluctuations and adjust the insulin delivery accordingly. As a result, it is important to integrate future delivery systems with glucose monitoring and online/offline analysis capabilities.

Meal Variability

Meal content and effect estimation are some of the least studied areas regarding contribution to glycemic variability. Correct estimation of carbohydrate contents of meals is, however, crucial if glycemic variability is to be minimized. People on insulin therapy are encouraged to focus on counting carbohydrates, especially when changing diet. **Figure 3A** shows the results from a study we did at Steno Diabetes Hospital in 2005, where 10 people with diabetes had to estimate carbohydrate contents of meals they had not self-prepared.[27] The % CV has been calculated compared to the predicted average and shows that people estimate very differently. The result showed a fairly high % CV of the different meal types, meaning that people were especially different in how to count carbohydrates in lunch, dinner, and snacks. Not surprisingly, breakfast had the least variability, probably due to its simple composition.

Figure 3B shows the average percentage error for two different carbohydrate estimation studies. Clearly, the study by Graf and colleagues[28] shows a large bias toward underestimation of most meals. The same pattern was not seen in our study. These studies show how difficult meal estimation can be and are one reason why people on bolus insulin have a tendency not to change their diet.

Studies showing variability in repeated meal responses with an exact carbohydrate count have been performed.[29] This implies that, even given an exact carbohydrate content, there can be a large difference in glycemic
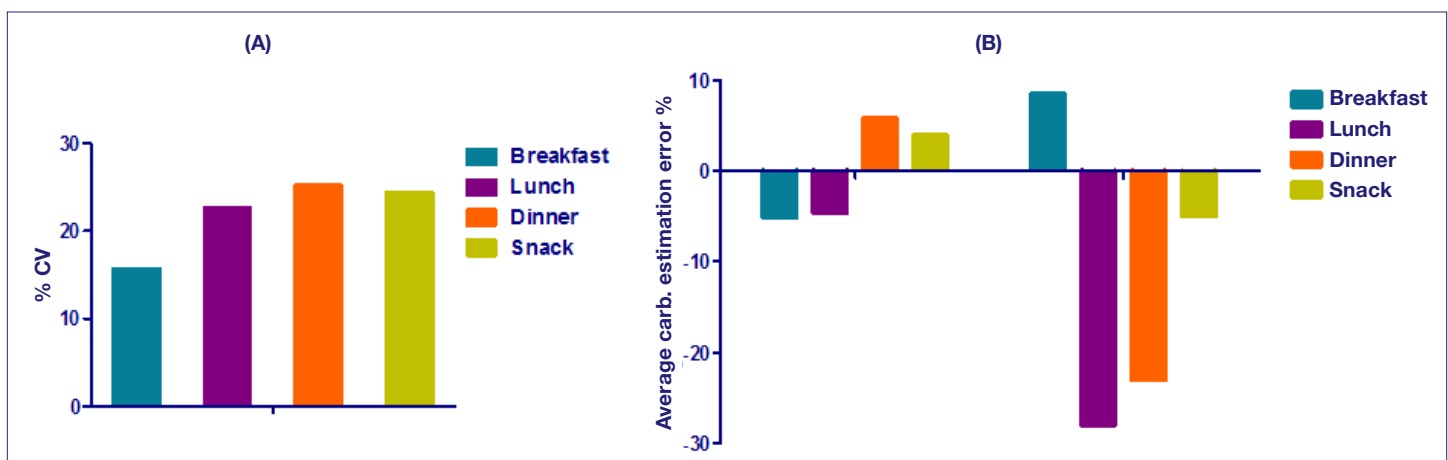
Figure 3. (**A**) Percent CV of estimated carbohydrate content in meals.[27] (**B**) Percent average error of estimated carbohydrate content in meals; the data on the left-hand side of the graph represent the results of Kildegaard and associates,[27] and the data on the right-hand side of the graph represent the results of Graff and coworkers.[28]

response to foods with different glycemic indexes. Besides this, day-to-day meal absorption is influenced by other factors, for instance, hunger.

No successful automatic system for carbohydrate estimation exists; however, some insulin pumps contain functionality for calculating the optimal meal bolus based on meal carbohydrate content. This is likely to be further developed in the future.

Lifestyle and Compliance

Being on insulin therapy requires focus and consistence in order to avoid and correct for glycemic fluctuations. This can, however, be a very difficult task. Exercise is, for instance, an important part of diabetes treatment, but even small intervals with changes in intensity can have significant effects for many hours.[23]

Even though modern delivery systems have improved in many ways, forgetting boluses does happen. In a study of children using insulin pumps, an average of 2.1 missed boluses per week was observed.[30] Another similar study on children showed how 38% of all children had missed more than 15% of their boli.[31] Obviously, this can explain hyperglycemic episodes; equally complicated, this sometimes calls for a correcting bolus, which can be difficult to predict.

Also, reporting food intake has shown to be difficult. People <120% ideal body weight miss reporting 10% of their diet, and people >120% Ideal body weight miss reporting 33%.[32] Another study showed how less than 59% of people report accurate diary intake defined by more than 90%.[33]

Some insulin pens include memory for storage of prior doses. Even though the idea of assisting people to remember injections is good, these systems have not been successful. The electronic capabilities of insulin pumps provide an ideal platform for electronic diaries, with possibilities for integration with other systems.

Glucose Monitoring Variability

The glucose monitor is one of the most important tools for glycemic regulation, with clear effects on long-term metabolic control.[34] Although laboratory tests have shown glucose meters to be accurate,[35,36] some studies have shown how accuracy can be a significant issue when in the hands of patients in their daily setting, as shown at **Figure 4**.[22,36] This is mostly because people contaminate
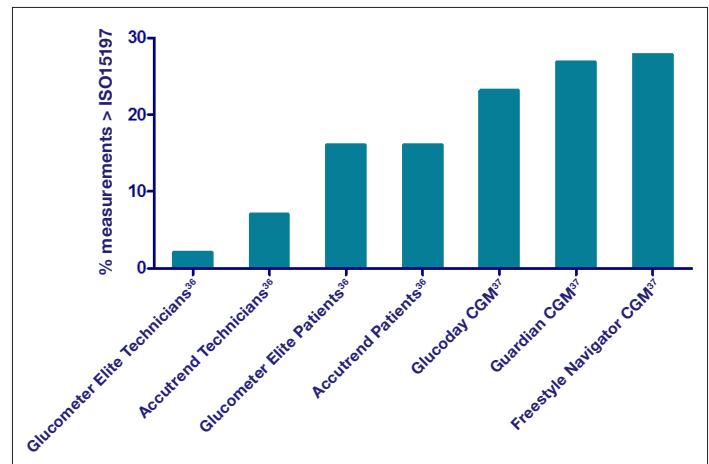
Figure 4. The percentage of measurements falling outside the ISO 15197 requirements for a number of strip-based glucose meters and CGM devices.

the blood samples or have difficulties handling the monitors.[22]

Figure 4 shows the error of several strip-based systems and continuous glucose monitors (CGMs) tested in two studies.[36,37] Numerous methods for evaluation of glucose measurement accuracy exist; however, for self-testing devices for managing diabetes, they have to be measured against the ISO15197 standard.[38] This standard states that (1) at a blood glucose level below 75 mg/dl, 95% of data should be ±15 mg/dl; and (2) at above 75 mg/dl, 95% of glucose should be ±20%. For system accuracy by least squares regression, 95% of the data should agree with the reference method and slope can only deviate by 65%.

Although CGM shows a larger error on **Figure 4**, it does provide additional information compared to strip-based systems and enables better glycemic control in people with type 1 and 2 diabetes.[39] For instance, CGM systems may be used for hypo alarms and could prevent hypos by turning off pumps.[40] One of the most beneficial outcomes of using CGM devices is that they have helped people better understand their blood glucose.[39]

Discussion

It is important to discriminate the involved variabilities in order to pinpoint therapy changes that can have important impact on glycemic predictability. Some of the variabilities are constant, some can be minimized, and some can be avoided.

Insulin variability is largely caused by intrinsic factors that cannot be easily changed. Minimized insulin

variability is achieved by moving to analogs combined with insulin pens or, even better, insulin pumps.

Even though people are taught to count carbohydrates, this is one of the most difficult tasks to do right and an area where no tools are available to provide an exact carbohydrate content of a meal in an easy way. If successfully invented, such a tool probably has the greatest potential to minimize glycemic variability.

Much can clearly be gained in glycemic predictability with increased focus on more frequent glucose readout, as it has been shown how hemoglobin A1c is reduced with the number of daily glucose measurements.[34] Continuous glucose monitor integration and analysis capability is therefore likely to become some of the most important future features in future insulin delivery systems.

The intrinsic factors influencing glycemic variability are more or less unalterable. People should be trained to be aware of the effect of counter-regulating mechanisms, as the dynamics can last for multiple hours. Exercise has many positive effects such as improved insulin sensitivity and loss of weight. Nevertheless, the effect of hard exercise can significantly trigger glucose dynamics and should therefore be considered.

Better compliance and a more stable lifestyle are key elements to improved glycemic stability. Compliance is often difficult because people themselves have to remember to take all injections and be aware of all snacks and meals. Fortunately, these problems have been recognized by the industry, and tools are appearing on the market to help, and pumps, glucose meters, and pedometers are beginning to integrate into electronic diaries and effective insulin management tools.[41]

Greater glycemic predictability can be achieved by modern diabetes technology; however, many elements can be further developed for great improvement in patient care.

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