Blood glucose control and monitoring in the critically ill
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Chapter 1
General Introduction and Outline of the Thesis
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Introduction

The pendulum of blood glucose control in critically ill patients

Intensive care unit (ICU) patients are admitted with or develop during admission hyperglycemia, which for years was thought to be an adaptive and foremost accurate response and thus left untreated [1]. However, at the beginning of this century several observational studies suggested that the occurrence of hyperglycemia was associated with worse outcome [2–6], and three randomized controlled trials showed that blood glucose control using insulin infusion targeting age–adjusted normoglycemia improved outcome of pediatric and adult ICU patients [7–9]. Consequently, this strategy was adopted in many ICUs worldwide, following international recommendations by several organizations including those by the Surviving Sepsis Campaign [10], the American Thoracic Society, the institute for Healthcare improvement, the Joint Commission on Accreditation of Healthcare Organization and the Volunteer Hospital Organization. Nevertheless consecutive randomized controlled trials challenged the benefits of insulin infusion targeting normoglycemia and even suggested harm from this approach. At least in part because many patients developed hypoglycemia under this strategy [11–15]. These results caused a shift from so–called ‘strict glucose control’ (i.e., targeting normoglycemia) to more moderate glucose control (i.e., preventing severe hyperglycemia). Regardless this change in the international recommendations regarding glucose control, currently many, if not all, ICU patients receive insulin infusions for shorter or longer periods during stay in the ICU [16, 17]. Very different from practice 15 years ago.

Practicalities of insulin infusion in critically ill patients

A large variety of factors may affect the efficacy and safety of insulin infusion, whatever blood glucose target is chosen. First, insulin infusion, or better said ‘insulin titration’, is a complex intervention that involves numerous sequential steps that all contain potential sources of variability. Without doubt, it requires adequate monitoring of the blood glucose level and as a result repeated blood glucose measurements. Furthermore, it requires a dedicated lumen of a central venous catheter for the infusion of insulin and an accurate syringe pump. Yet the most critical factor perhaps is an experienced ICU nurse for delicate adoptions of the infusion rate at the bedside [18].

Domains of blood glucose control in critically ill patients

The targets of blood glucose control have been, and still are, subject of many discussions. Notably, blood glucose control is more than a simple ‘targeting normoglycemia’ or ‘preventing hyperglycemia’ alone as there are more domains of blood glucose control. This seems to be associated with the outcome of critically ill patients.

First, ‘hypoglycemia’ is a feared complication of treatment with insulin because severe and perhaps even mild hypoglycemia has been found to be associated with a worse outcome in critically ill patients [19, 20]. Therefore, it is generally considered of utmost importance that hypoglycemia is corrected as soon as possible [21]. However, it has been suggested that not hypoglycemia itself is harmful. Several preclinical and clinical studies suggest that a transition from hypoglycemia to hyperglycemia could be detrimental and possibly more harmful than hypoglycemia itself [22–24]. Indeed, a preclinical study in rodents showed that brain damage was not associated
with severe hypoglycemia, but with the overcorrection of the blood glucose level [24]. Moreover, in healthy humans and non–critically ill diabetes patients transition of hypoglycemia to hyperglycemia is associated with hampered endothelial function, increased oxidative stress, activation of thrombosis and inflammation [22, 23].

Second, rapid and large fluctuations of the blood glucose level, or increased ‘glycemic variability’, are also associated with increased mortality in critically ill patients [25, 26]. In diabetic patients high glycemic variability is associated with increased oxidative stress [27]. Similar associations have been found in critically ill patients [26, 28].

Notably, there is an additive detrimental effect of high glycemic variability, low blood glucose level and high median blood glucose in ICU patients [26]. Thus, on top of ‘targeting normoglycemia’ or ‘preventing hyperglycemia’, one should add ‘prevention of hypoglycemia’ and ‘increased glycemic variability’ as targets of blood glucose control in ICU patients [29].

**Blood glucose monitoring in critically ill patients**

Accurate and frequent blood glucose measurements are imperative for effective and safe insulin titration. Presently in the ICU, glucose levels are monitored manually through intermittent measurements of the blood glucose level in central laboratories or using laboratory–based blood gas analyzers and/or glucose strips at the bedside [17, 29]. Yet intermittent manual blood glucose monitoring is impractical, expensive, time – and blood consuming [30] and could even cause dangerous insulin titration errors in ICU patients [31]. Glucose monitoring through so–called ‘continuous’ glucose monitoring (CGM) could overcome some of the shortcomings and drawbacks of intermittent manual glucose monitoring. Probably, CGM could allow for more accurate adjustments in the insulin infusion rate based on trends of the glucose level visualized on a monitor. Several CGM devices for use in the ICU are currently being developed. However, these all require thorough accuracy testing in diverse cohorts of critically ill patients before they can be implemented in daily ICU practice. Then it must be determined if use of CGM indeed improves efficacy and safety of blood glucose control using insulin.

**Aims of this thesis**

This thesis has three key aims: (1) to summarize practical aspects and metrics of blood glucose control (**part I**), (2) to discuss factors that could affect efficacy and safety of blood glucose control (**part II**) and (3) to discuss features of blood glucose monitoring (**part III**).
### Definitions used in this thesis

In this thesis the following definitions are used, unless stated otherwise:

<table>
<thead>
<tr>
<th>Term</th>
<th>Definition</th>
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<tbody>
<tr>
<td>‘Blood glucose level’</td>
<td>Glucose level measured in arterial, capillary of venous blood</td>
</tr>
<tr>
<td>‘Blood glucose control’</td>
<td>Any strategy that aims to control the blood glucose level</td>
</tr>
<tr>
<td>‘Blood glucose control using insulin infusion’</td>
<td>Control of the blood glucose level by using intravenous infusion of insulin, in most cases actrapid or novorapid</td>
</tr>
<tr>
<td>‘Blood glucose control using insulin infusion targeting normoglycemia’</td>
<td>Sometimes called ‘intensive insulin therapy’ [7–9, 11, 15, 32] or ‘strict glycemic control’ [12] or ‘tight glycemic control’ [13, 14, 33], aiming for (age–adjusted) normoglycemia</td>
</tr>
<tr>
<td>‘Blood glucose control using insulin infusion preventing hyperglycemia’</td>
<td>Sometimes called ‘loose’ or ‘moderate’ blood glucose control [18, 34], aiming for a certain blood glucose level other than normoglycemia</td>
</tr>
<tr>
<td>‘Insulin’</td>
<td>Hormone which is most known for the glucose lowering effect, insulin–analoges are almost similar to human insulin</td>
</tr>
<tr>
<td>‘Insulin infusion’</td>
<td>Continuous intravenous administration of insulin, in most cases actrapid or novorapid</td>
</tr>
<tr>
<td>‘Insulin titration’</td>
<td>The delicate process of adjusting insulin infusion rates to achieve a certain blood glucose level, mostly performed by (experienced) ICU nurses</td>
</tr>
<tr>
<td>‘Normoglycemia’</td>
<td>Blood glucose levels in the range of normal fasting blood glucose levels (i.e., 80-110 mg/dL)</td>
</tr>
<tr>
<td>‘(Severe) hyperglycemia’</td>
<td>Blood glucose levels in ranges like &gt; 140 mg/dL, &gt; 150 mg/dL, &gt; 180 mg/dL or higher</td>
</tr>
<tr>
<td>‘(Severe) hypoglycemia’</td>
<td>Blood glucose levels in ranges like &lt; 80 mg/dL, &lt; 70 mg/dL, &lt; 40 mg/dL and &lt; 20 mg/dL</td>
</tr>
<tr>
<td>‘Blood glucose variability’</td>
<td>Sometimes called ‘glycemic variability’, fluctuations of the blood glucose level, for which several metrics are suggested; most often the standard deviation (or SD) of the blood glucose level</td>
</tr>
<tr>
<td>‘Glucose complexity’</td>
<td>More subtle fluctuations of the blood glucose level, compared to the fluctuation captured in metrics of ‘blood glucose variability’</td>
</tr>
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</table>
‘Insulin variability’

Suggested changes of the insulin infusion rate glucose level, for which so far no metric has been

‘Point of care blood glucose measurement’

Any blood glucose measurement, which is performed outside a central laboratory, i.e., at the bed–side or close to the bed–side (i.e., in the ICU department)

‘Continuous glucose monitoring’

A monitoring system consisting of a sensor or more sensors, a processor and a monitor, showing changes in a glucose level in a continuous fashion.

Short outline of this thesis

In chapter 5 it was hypothesized that blood glucose control changed after publication of the NICE–SUGAR trial in ICUs in the Netherlands [13]. To test this hypothesis, we performed (a) a survey on changes in the local guidelines for blood glucose control, and (b) collected all blood glucose measurements during the entire stay in ICU to calculate several metrics for blood glucose control.

In chapter 6, it was hypothesized that a history of diabetes would attenuate the strength of associations between dysglycemia and mortality of ICU patients. A retrospective analysis of prospectively collected data of patients admitted in 23 ICUs from 12 countries was performed to test this hypothesis.

In chapter 7 it was hypothesized that a transition from hypoglycemia to hyperglycemia is independently associated with ICU mortality of critically ill patients. The study used cohorts of patients under ‘strict glucose control’ and ‘moderate’ glucose control in seven Dutch ICUs. Three metrics for glucose variability were calculated from blood glucose levels obtained early after hypoglycemia.

In chapter 8, it was hypothesized that bolus infusion of hydrocortisone increases glucose variability and insulin variability. This study used a cohort of critically ill patients admitted to a single Dutch ICU.

In chapter 9 and chapter 10 two different CGM systems were tested for their point accurate and reliability in critically ill patients in two prospective single–center studies.

In chapter 11 the costs of point of care testing of the blood glucose level was calculated for three ICUs in the Netherlands.

Finally, the results from the abovementioned studies are summarized and discussed in chapter 12 (with a translation into Dutch in chapter 13).

References

5. Finney SJ, Zekveld C, Elia A, Evans TW:


22. Ceriello A, Novials A, Ortega E, La Sala L, Pujadas G, Testa R, Bonfigli AR, Esposito K, Giugliano D: Evidence that hyperglycemia after recovery from hypoglycemia worsens endothelial function and increases oxidative stress and inflammation in healthy control


