In-hospital glycaemic control: A bittersweet symphony

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Publication date
2015
Document Version
Final published version

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Marjolein Sechterberger

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COLOFON

In-hospital glycaemic control - a bittersweet symphony.
Dissertation, University of Amsterdam, Amsterdam.

ISBN	978-94-6233-044-3
Author	Marjolein K. Sechterberger
Cover	Luite van Assen
Lay-out	Marjolein K. Sechterberger
Print	Gildeprint

The printing of this thesis was financially supported by:
NovoNordisk B.V., Chipsoft B.V., Goodlife Healthcare B.V., Abbott Diabetes Care, Sanofi-Aventis Netherlands B.V., B.Braun Medical B.V., Teaching hospital OLVG, Stichting Wetenschap en Onderzoek Interne Geneeskunde OLVG, Stichting Asklepios and University of Amsterdam.

IN-HOSPITAL GLYCAEMIC CONTROL

a bittersweet symphony

ACADEMISCH PROEFSCHRIFT

ter verkrijging van de graad van doctor

aan de Universiteit van Amsterdam

op gezag van de Rector Magnificus

prof. dr. D.C. van den Boom

ten overstaan van een door het College voor Promoties ingestelde commissie,

in het openbaar te verdedigen in de Agnietenkapel

op vrijdag 4 september 2015, te 14.00 uur

door Marjolein Katinka Sechterberger

geboren te Doetinchem

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‘Cause it’s a bittersweet symphony, this life.

(M. Jagger/K. Richards/R. Ashcroft)

Voor mijn moeder

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Introduction

M.K. Sechterberger

In 1849, the French physiologist Claude Bernard conducted a rather invasive experiment: with a needle he punctured the floor of the fourth brain ventricle of a rabbit.[1] The effect of this puncture was an impressive rise in blood glucose and within an hour the urine of the rabbit contained abundant glucose. The hyperglycaemia produced by this 'piqûre diabetique', or 'diabetes puncture' was exceedingly interesting: glucose only rose temporarily, never lasting more than one day.[1] Therefore, it could hardly be called 'diabetes'. How to interpret these findings?

One may be curious as to the reason to conduct this experiment. A year earlier, Bernard had discovered that the liver itself was a source of glucose[1], something so far unknown. With his experiment he tried to find out what was controlling the release of glucose from the liver. With Bernards' hypothesis that chemical functions of the body were often under the control of the nervous system, he decided to see what would happen if he stimulated the vagus nerve. The floor of the fourth ventricle was where the vagus nerve (as well as other sympathetic nerve fibers) were known to originate.

Bernards' first thoughts that hyperglycaemia resulted from stimulation of the origin of the vagus nerve were soon rebutted. Bernard proved himself wrong by his finding that transection of the vagus nerve before his 'piqûre diabetique' did not prevent hyperglycaemia. He concluded that the effect was mediated by the sympathetic system[1], in which he was mainly correct. Many decades later it was shown that sympathetic stimulation results in release of adrenaline from its nerve endings.[2] Thus, adrenaline secondarily promotes glucose discharge from the liver.

Acute hyperglycaemia or 'stress-induced hyperglycaemia', whether or not the patient has a history of diabetes mellitus, has now been recognized to be a frequent concomitant of a pathophysiological stressor, such as acute injury ('puncture'), surgery or critical illness.[3,4] It is intriguing to realize that Claude Bernard was actually the first to report the occurrence of hyperglycaemia following 'acute injury'.

Stress-induced hyperglycaemia: friend or foe?

Hyperglycaemia in acute illness results from a combination of enhanced hepatic glucose production (increased gluconeogenesis due to the release of counterregulatory hormones) and decreased peripheral glucose utilization (insulin resistance)[3,4] (*Figure 1*). Historically, hyperglycaemia was considered as a normal response to stress. Until the 21th century, it was considered state of the art to tolerate glucose levels up to 12 mmol/L in critically ill patients.[5] Hyperglycaemia was thought to be beneficial for organs that solely rely on

glucose for their energy supply. In recent decades, the idea evolved that acute hyperglycaemia in acute illness was not that beneficial. Similarly to patients with diabetes,

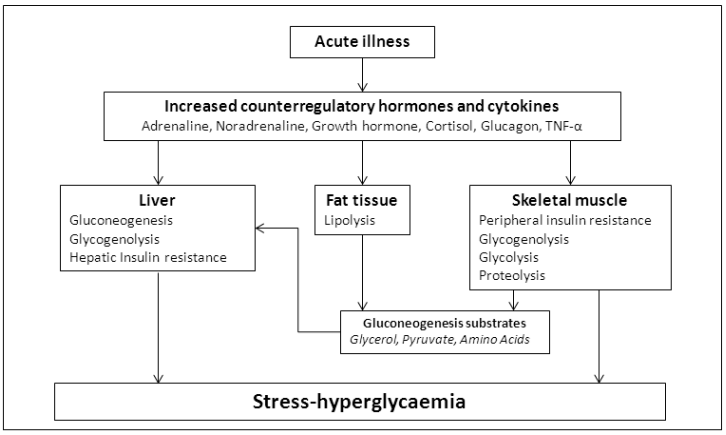

Figure 1 Stress hyperglycaemia in critical illness

prolonged hyperglycaemia in critical illness leads to several adverse reactions, such as endothelial damage, increased susceptibility to infections and deranged inflammatory and coagulation responses, which in turn exacerbate critical illness.[4] Moreover, hyperglycaemia in critically ill patients has been shown to independently increase the risk of hospital mortality.[6]

1

Strict glycaemic control

The large randomized controlled 'Leuven' trial[7] conducted in 2001 was the first of a series of investigations that assessed the effect of strict glycaemic control (glucose target < 6 mmol/L) with insulin therapy on morbidity and mortality in critically ill patients. The Leuven trial found an impressive 42% reduction in mortality in critically ill patients in the strict glycaemic control group, which resulted in worldwide guidelines promoting 'tight' glucose control. Nevertheless, subsequent studies could not reproduce these highly promising results, culminating in the largest multicenter NICE-SUGAR study[8], that suggested that a moderate glycaemic target was preferable to 'tight' glucose control. Furthermore, several major concerns of insulin therapy for the treatment of stress-induced hyperglycaemia were revealed, such as an increased risk of hypoglycaemia[9,10] and more pronounced glucose variability (swings in blood glucose level)[11]. In addition, both hypoglycaemia and glucose variability were shown to be associated with increased risk of ICU mortality.[9,11] The current consensus is that hyperglycaemia should be corrected, while avoiding hypoglycaemia and high glucose variability.[12] Notwithstanding, there is still uncertainty among clinicians on how to best control 'inpatient dysglycaemia'—hyperglycaemia, hypoglycaemia and increased glucose variability.

How can we best optimize in-hospital glycaemic control? This thesis further explores epidemiology and treatment of in-hospital dysglycaemia, as well as the usefulness of glucose monitoring techniques to control in-hospital dysglycaemia.

Thesis Outline

Chapter 2 gives an overview of and comments on the results of several major studies which investigated the effect of glycaemic control with insulin therapy in hospitalized patients admitted to the intensive care unit (ICU), coronary care unit and general wards.

Although a clear association between the three dysglycaemic states (hyperglycaemia, hypoglycaemia and glucose variability) and ICU mortality exist,[6,9,11] it is unknown whether a diagnosis of diabetes mellitus affects these associations. In **chapter 3**, we describe a large observational cohort study performed to examine the relationship of diabetic status to four measures of glycaemic control—mean glucose, glucose variability, hypoglycaemia (<2.2 mmol/L), and low glucose (2.3 to 4.7 mmol/L)—and ICU mortality.

By the results of the previous study, which clearly showed that a diagnosis of diabetes affects the association between 3 out of 4 measures of glycaemic control and ICU mortality[13], another research question emerged. Although the course of disease of type 1 and type 2 diabetes differs, the distinction between the specific type of diabetes is rarely made when these patients are admitted to the ICU. This may lead to inaccurate interpretations with regard to glycaemic control in the ICU. Therefore, diabetes patients, admitted to the ICU and included in the observational study as described in chapter 3, were retrospectively classified as type 1 or type 2 diabetes patients. **Chapter 4** describes patient- and admission-related characteristics between type 1 and type 2 diabetes patients in relation to glycaemic control.

ICUs worldwide almost universally measure blood glucose levels intermittently using either point-of-care glucose meters or blood gas analyzers[14]. This often leads to a considerable workload for the intensive care nurses. In addition, information about the glucose levels is lacking for the period in-between measurements with possible unnoticed hypoglycaemic episodes. Continuous glucose monitoring (CGM) could be of value to facilitate or improve glycaemic control. In **Chapter 5**, a randomized controlled design was used to compare the safety and efficacy of CGM-driven glucose regulation by using a subcutaneous CGM device, with point-of-care driven glucose regulation. In addition, nursing workload and the daily costs for glucose control were assessed.

There is increasing interest in developing new technologies to monitor blood glucose levels in critically ill patients.[14] One of these new technologies is measuring arterial glucose levels by fluorescence techniques.[15] Theoretically, intra-arterial positioning of CGM devices could yield frequent, immediate and accurate glucose readings. Moreover, arterial access is frequently obtained in ICU patients and would be convenient to use also for continuous glucose monitoring. **Chapter 6** describes accuracy results of two CGM devices, the GluCath® intra-arterial continuous glucose monitoring (IA-CGM) system and the FreeStyle Navigator® subcutaneous continuous glucose monitoring (SC-CGM) system, in post-cardiac surgery patients admitted to the ICU.

Glucose variability is clearly related to mortality in critically ill patients without diabetes.[11] Moreover, it has been identified as a predictor of hypoglycaemia.[16] With the increased availability of CGM in both the outpatient and inpatient settings, clinicians would benefit from an easy-to-understand metric to quantify glucose variability. Over the years, numerous measures have been proposed to quantify glucose variability, but most of them are not useful in clinical practice.[17] The most popular metric to quantify glucose variability is the mean amplitude of glycaemic excursions (MAGE).[18] The ‘‘ruler and pencil’’ approach to calculate MAGE is operator-dependent and time-consuming for analysis of continuous glucose monitoring data. Therefore, several computer software programs have been developed for the automated calculation of MAGE. In **chapter 7**, the agreement of currently available MAGE calculators was evaluated.

1

The last two chapters focus on the consequences of stress-induced hyperglycaemia on coagulation activation. It is known that venous thromboembolism, including deep vein thrombosis and pulmonary embolism, is often accompanied by acute hyperglycaemia.[4] Two explanations for the presence of stress-hyperglycaemia during venous thromboembolism can be considered: (1) elevated blood glucose levels during a VTE can result from the physical stress response induced by the VTE event itself, and (2) undiagnosed impaired glucose tolerance may be present in a proportion of patients before the VTE itself and may therefore have contributed to the development of thrombosis. As stress hyperglycaemia may be considered as a manifestation of impaired glucose tolerance, which in itself frequently evolves into diabetes, one would expect an increase in incidence rate of diabetes in patients after a diagnosis of VTE. In **Chapter 8** we report on a population-based registry study performed to test the hypothesis that the risk of diabetes in subjects with pulmonary embolism is increased compared with subjects without pulmonary embolism.

Hyperglycaemia is common in patients undergoing hip surgery. In addition, the risk to develop venous thromboembolism postoperatively is considerable in orthopaedic surgery patients.[19] A previous small observational study has shown that hip surgery-induced hyperglycaemia is followed by a proportional change in coagulation parameters.[20]

Furthermore, additional observational data including almost 7,000 hip surgery patients showed that stress-induced hyperglycaemia following hip surgery was independently associated with venous thromboembolism.[21] Whether glucose lowering therapy in hip surgery patients with stress-induced hyperglycaemia influences coagulation activation is as yet unknown. In **chapter 9** we report on an intervention study performed to assess the efficacy of the human GLP-1 analogue liraglutide, a once-daily fixed dose glucose lowering agent, to lower glucose during and after hip surgery and its influence on coagulation activation.

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In-Hospital Hyperglycaemia: Quo Vadis?

M.K. Sechterberger, S.E. Siegelaar, J.H. DeVries

Diabetes Technology & Therapeutics 2011; 13(11):1081-4.

After a decade of clinical research investigating the optimal treatment of hyperglycaemia in critically ill patients, the matter is still not settled. Since the publication of the first Leuven study in 2001[1], which showed that normalization of hyperglycaemia by intensive insulin treatment with a targeted blood glucose of 4.4–6.6 mmol/L compared with conventional glycaemic control (glucose target, 10–11.1 mmol/L) resulted in an absolute reduction in mortality (4.6% vs. 8%, $P < 0.04$) in a surgical intensive care unit (ICU), subsequent trials have added confusion, rather than confirmed these initial findings. The many clinical trials and interventions set up to confirm the benefit of normalizing hyperglycaemia in different clinically ill populations failed to do so[2-5] and suggested that results may differ between admission diagnosis[6-9], between type of ICU[2,4,5,10,11], or between patients with or without previously diagnosed diabetes.[1–4,10,12,13]

The largest and perhaps most important trial was the multicenter randomized controlled NICE-SUGAR study in 2009.[10] Contrary to expectations, these investigators did not confirm the previous findings of the Leuven trials; moreover, they showed an increase in 90-day mortality from 24.9% to 27.5% ($P = 0.02$) in the intensive insulin therapy group (glucose target, 4.5–6.0 mmol/L) compared with standard therapy (glucose target, < 10 mmol/L) in a mixed ICU population. In addition, there was an increase in the incidence of hypoglycaemia in the intensive insulin therapy group compared with the conventional-control group (6.8% vs. 0.5%, $P < 0.001$).

Why all these different outcomes from different studies? Several possibly important methodological differences (i.e., different target ranges of blood glucose in the intervention group and the control group, differences in methods used for blood glucose measurements, and different sampling sites) may have contributed to the different outcomes.[14] The more attractive explanation for the different outcomes, however, is the differences in feeding strategies in the major clinical trials.[15] The high amount of parenteral nutrition used in the Leuven trials, compromising a higher total glucose load compared with enteral nutrition, may have increased the severity of stress-induced hyperglycaemia, and thus intensive insulin treatment may merely have contravened a side effect of parenteral nutrition. In contrast, tight glycaemic control in patients receiving enteral nutrition, as was the feeding strategy used almost exclusively in the NICE-SUGAR study[10] seems to be harmful, possibly because there is an increased risk of hypoglycaemia. The results of the meta-regression analysis of Marik and Preiser[15] suggest that intensive insulin treatment is only of benefit in patients receiving parenteral nutrition, and particularly so in those with a low severity of illness.

Recently, the EPaNIC study[16] compared two feeding strategies in the context of normoglycaemia in critically ill patients. They compared early initiation of parental

feeding, as supplement to enteral nutrition, thereby preventing a caloric deficit in critical illness (the early-initiation group), with withholding parental feeding during 1 week (the late-initiation group). The late initiation of parental feeding appeared to be superior; specifically, the study found a significantly shorter median duration of hospital stay (relative increase of 6.3% in the likelihood of being discharged earlier from hospital [95% confidence interval, 1.00–1.13; P = 0.04]) and significantly fewer complications (22.8% vs. 26.2%, P = 0.008). It is important to mention that this study targeted a blood glucose level of 4.4–6.1 mmol/L and that the glucose target level achieved was almost the same in the two groups (5.7 ± 0.8 mmol/L in the late-initiation group vs. 5.9 ± 1.0mmol/L in the early-initiation group). It remains unclear whether an intermediate blood glucose target, as recommended nowadays, would have affected the outcome of this trial.

Returning to how to translate the contradictory outcomes of the different trials into clinical practice, consensus grew that an intermediate blood glucose target range would be beneficial. Siegelaar et al.[11] provided epidemiological support for this and showed in a retrospective database cohort study that there is a U-shaped curve relationship between mean glucose and mortality during ICU stay in a mixed ICU population. Hence, a ''safe range'' for mean glucose between 7.0 and 9.0 mmol/L could be defined. Such an increase in the blood glucose target range is very likely to diminish the incidence of hypoglycaemia at the same time. Of note is that Hermanides et al.[17] showed that hypoglycaemia, even with adjustment for severity of disease using the daily assessed Sequential Organ Failure Assessment score, is related to an increase in ICU death. The defined ''safe'' blood glucose range by Siegelaar et al.[11] and the importance of diminishing hypoglycaemia are in line with the present recommendations for in-hospital glucose targets from the American College of Physicians[18] and the American Association of Clinical Endocrinologists and American Diabetes Association[19] to maintain a medium high glucose level (7.8–11.1 and 7.8–10.0 mmol/L, respectively) and to avoid hypoglycaemia.

Unfortunately, contradiction in the outcomes of clinical trials, as described above, is not uncommon. It generates substantial uncertainty for clinical practitioners and for experts who develop guidelines. Professional societies immediately issued guidelines on target glucose levels in critically ill patients after the report on the initial Leuven study in 2001.[1] However, with publication of the results of subsequent studies, most professional societies have adjusted their guidelines by increasing the glucose target range. With hindsight, professional societies were too hasty to integrate the results of an early, single-center, non-blinded study, such as the Leuven trial[1], into their clinical guidelines. It is important to mention, and also as a cautionary note to the authors and the readers of these guidelines, that even very highly cited randomized controlled trials may be refuted over the time.[20] Of note is that the workload associated with establishing tight glycaemic control is substantial.

However, defining the glucose target range by ending up in the middle between the Leuven and NICE-SUGAR criteria may be somewhat of a poor man's answer. How do we know that higher targets aren't even better? Or can we even be sure that stress hyperglycaemia should be treated at all? Presently, these questions are still unanswered. The only solution would be a three-armed randomized trial comparing strict, less strict, and minimal glycaemic control in different critically ill populations. The number of patients needed in this trial would be immense, and so will be the cost. Therefore, it may well be that such a trial will never be performed.

Although many researchers have focused on glycaemic control in critically ill patient populations in an ICU setting, another interesting question is whether tight glycaemic control in the coronary care unit would be beneficial. The initial concept—that metabolic modulation of acute myocardial infarction (AMI) by energy supply with glucose–insulin–potassium (GIK) infusion would improve the outcomes in patients suffering from acute coronary disease[21]—was ultimately studied by the large multicenter randomized controlled CREATE-ECLA trial.[22] These researchers found that high-dose GIK infusion in patients with acute ST-elevation myocardial infarction did not have a beneficial effect on mortality rate (10% in the GIK infusion group vs. 9.7% in the control group, P = 0.45). This trial and a subsequent metaanalysis by Puskarich et al.[23] rejected the thought that GIK infusion is beneficial in the treatment of AMI. However, this trial was not designed for glucose control as a primary target, which is important because GIK generally increases glucose concentrations.

Other studies focused on achieving normoglycaemia by glucose control with intensive insulin therapy. The DIGAMI study[24], published in 1995, showed a 1-year mortality rate reduction of 29% (P = 0.027) in diabetes patients after an AMI using intensive insulin treatment. However, subsequent studies as the DIGAMI-2 trial[25] and the HI-5 study[8] failed to replicate this result, possibly because these studies were hampered by limited sample sizes. Moreover, since the development of improved reperfusion treatments (i.e., percutaneous coronary intervention) has contributed to an impressive decrease in mortality in patients with AMI[26] and because of the substantial variability in insulin treatment rates across medical centers in a coronary care unit setting[27], there is a need to confirm the possible benefits of glucose lowering in populations both with and without diabetes treated with state-of-the-art interventions.

Few clinical trials have focused on the optimal management of glycaemic control at the ward. Recently, the RABBIT 2 surgery trial[28] investigated the efficacy and safety of a basal–bolus insulin regimen compared with sliding-scale regular insulin in patients with type 2 diabetes admitted to general surgery wards. They showed a significant improvement

in glycaemic control in the basal–bolus insulin group compared with the sliding-scale regular insulin group ($P < 0.01$), with a lower mean fasting glucose (8.6 – 2.1 vs. 9.2 – 2.2 mmol/L, $P = 0.037$) and a lower mean daily glucose during the hospital stay (8.7 – 1.8 vs. 9.8 – 2.4 mmol/L, $P < 0.001$). Also, perioperative complications, defined as a composite end point including wound infection, pneumonia, bacteremia, respiratory failure, and acute renal failure, was significantly reduced in the basal–bolus treatment group (8.6% vs. 24.3%, $P = 0.003$). These results are in accordance with the recommendation of the American Association of Clinical Endocrinologists and American Diabetes Association guideline,[19] that scheduled subcutaneous administration of insulin is the preferred method for achieving and maintaining glucose control in noncritically ill patients. Prolonged therapy with sliding-scale regular insulin is discouraged. The blood glucose targets recommended by the American Association of Clinical Endocrinologists and American Diabetes Association guideline[19] on medical or surgical wards in non-critically ill patients treated with insulin are premeal blood glucose values < 7.8 mmol/L in conjunction with random blood glucose values < 10 mmol/L, as long as these targets can be safely achieved. As mentioned in the guideline, these targets are based on clinical experience and judgment. The blood glucose values achieved in the RABBIT 2 surgery trial[28] indicate that these targets are not easily met, and there is a lack of evidence to support the treatment of patients without diabetes on the ward with insulin.

In conclusion, a decade of intensive clinical research did not provide us with a clear and simple answer to the complex problem of in-hospital glycaemic control. Although the current consensus to maintain a medium-high glucose level in an ICU setting is reasonable, we emphasize that further clinical research toward in-hospital glycaemic control in noncritically ill patients is warranted.

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3

The effect of diabetes on the association between measures of glycaemic control and ICU mortality: a retrospective cohort study

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Critical Care 2013 Mar 19;17(2):R52.

Abstract

Background

In critical illness, four measures of glycaemic control are associated with ICU mortality: mean glucose concentration, glucose variability, the incidence of hypoglycaemia (≤ 2.2 mmol/L) or low glucose (2.3 to 4.7 mmol/L). Underlying diabetes mellitus (DM) might affect these associations. Our objective was to study whether the association between these measures of glycaemic control and ICU mortality differs between patients without and with DM and to explore the cut-off value for detrimental low glucose in both cohorts.

Materials and Methods

This retrospective database cohort study included patients admitted between January 2004 and June 2011 to a 24-bed medical/surgical ICU in a teaching hospital. We analysed glucose and outcome data from 10,320 patients: 8,682 without DM and 1,638 with DM. The cohorts were subdivided into quintiles of mean glucose and quartiles of glucose variability. Multivariable regression models were used to examine the independent association between the four measures of glycaemic control and ICU mortality, and for defining the cut-off value for detrimental low glucose.

Results

Regarding mean glucose, a U-shaped relation was observed in the non-DM cohort with an increased ICU mortality in the lowest and highest glucose quintiles (odds ratio = 1.4 and 1.8, $P < 0.001$). No clear pattern was found in the DM cohort. Glucose variability was related to ICU mortality only in the non-DM cohort, with highest ICU mortality in the upper variability quartile (odds ratio = 1.7, $P < 0.001$). Hypoglycaemia was associated with ICU mortality in both cohorts (odds ratio non-DM = 2.5, $P < 0.001$; odds ratio DM = 4.2, $P = 0.001$), while low-glucose concentrations up to 4.9 mmol/L were associated with an increased risk of ICU mortality in the non-DM cohort and up to 3.5 mmol/L in the DM cohort.

Conclusion

Mean glucose and high glucose variability are related to ICU mortality in the non-DM cohort but not in the DM cohort. Hypoglycaemia (≤ 2.2 mmol/L) was associated with ICU mortality in both. The cut-off value for detrimental low glucose is higher in the non-DM cohort (4.9 mmol/L) than in the DM cohort (3.5 mmol/L). While hypoglycaemia (≤ 2.2 mmol/L) should be avoided in both groups, DM patients seem to tolerate a wider glucose range than non-DM patients.

Introduction

Hyperglycaemia, hypoglycaemia and increased glucose variability in critically ill patients are independently associated with ICU mortality.[1–6] In the last decade many clinical triallists have attempted to improve mortality rates through intensive insulin therapy. Unfortunately, these trials have produced conflicting data, with some of the studies showing lower and others higher mortality with strict glucose control, the latter possibly due to an increased incidence of hypoglycaemia.[7–12] There is consensus about the importance to avoid hypoglycaemia and many ICUs have therefore increased their lower glucose limit.[13] However, there is no consensus about the optimal target glucose range.

In a previous database cohort study, we found an optimal mean glucose range of 6.7 to 8.4 mmol/L in a medical cohort and 7.0 to 9.4 mmol/L in a surgical cohort.[14] We additionally found that glucose concentrations that were low but above hypoglycaemic levels (between 2.3 and 4.7 mmol/L) were associated with increased ICU mortality.[3] Thus, in addition to the mean glucose concentration, glucose variability and hypoglycaemia, a fourth measure of glycaemic control—low glucose (2.3 to 4.7 mmol/L)— is associated with ICU mortality in the critically ill.

Underlying diabetes mellitus (DM) might affect the abovementioned associations. In a recent review we examined the current literature on glycaemic control and mortality in diabetic ICU patients and we found that, despite patients with DM having an increased risk of developing complications when admitted to the ICU, their risk of mortality is not increased.[15] In addition, ICU patients with DM have lower mortality in the higher mean glucose range compared with those without DM, although varying cut-off values were used.[16–19] Some studies found the opposite, with higher mortality rates for DM patients in the low-normal mean glucose range. However, these findings were unadjusted results only[18,20] and this relation was not significant after adjustment for severity of disease.[16] Furthermore, high glucose variability in ICU patients with DM seems to be less harmful than in patients without DM[21,22] although data are limited. Lastly, hypoglycaemia is associated with mortality in patients with and without DM,[3,4,23] while the risk of hypoglycaemia is higher in patients with DM.[4,24] Altogether, some of the abovementioned findings are inconsistent and none of the reviewed studies evaluated all four measures of glycaemic control concomitantly.

The objective of this study was to determine whether the association between measures of glycaemic control—mean glucose, glucose variability (measured as the mean absolute glucose (MAG) change), the occurrence of hypoglycaemia (≤ 2.2 mmol/L) or low glucose (2.3 to 4.7 mmol/L)—and ICU mortality differs between patients without and with underlying DM in a large cohort of critically ill patients admitted to a general ICU of a

teaching hospital in the Netherlands. We also explored the cut-off value for detrimental low glucose in both populations.

Materials and methods

Design and setting

The current study was conducted as a single-centre retrospective database cohort study in a 24-bed mixed surgical/ medical ICU in a teaching hospital (Onze Lieve Vrouwe Gasthuis, Amsterdam, the Netherlands). All data were collected prospectively. All beds were equipped with a clinical information system (MetaVision; iMDsoft, Tel Aviv, Israel) from which clinical and laboratory data were extracted. The nurse-to-patient ratio was on average 1:2, depending on the severity of disease. According to national guidelines this research is exempt from ethical approval because it is a retrospective study. The requirement for informed consent was waived because all data were anonymous and collected retrospectively.

Glucose regulation protocol

A glucose regulation protocol, with a target blood glucose concentration of 4.0 to 7.0 mmol/L, was implemented in 2001 after the publication of the study by van den Berghe and colleagues.[7] The glucose regulation sliding scale algorithm was connected to the clinical information system and fully computerised with an integrated decision support module controlling the algorithm.[25] The glucose regulation protocol has been reported previously.[2,3,14] In April 2009, following the publication of the Normoglycaemia in Intensive Care Evaluation – Survival Using Glucose Algorithm Regulation investigators in 2009[11], a new target blood glucose concentration of 5.0 to 9.0 mmol/L was instituted. To date, this new target blood glucose range is maintained in routine intensive care management.

Cohort and data collection

Relevant data were extracted from the clinical information system concerning patients admitted to the ICU between January 2004 and June 2011. Readmissions, patients with a withholding care policy, and patients with < 3 glucose values during ICU admission were excluded. The assignment of each patient's diabetic status on ICU admission was based on the use of oral glucose-lowering drugs and/or insulin therapy. Demographic variables, admission diagnosis, glucose values, the occurrence of hypoglycaemia and ICU and hospital mortality rates were assessed. Severity of disease was assessed using the Acute Physiology and Chronic Health Evaluation (APACHE) II score on admission.[26] For each subsequent day of ICU admission, the Sequential Organ Failure Assessment score was assessed as a measurement of severity of disease.[27] The maximal Sequential Organ Failure Assessment score was determined for the patient's entire stay in the ICU.[28]

Glucose measurements

Glucose was measured from blood samples obtained from an arterial catheter using the Accu-chek (Roche/ Hitachi, Basel, Switzerland). Results were automatically stored in the clinical information system. For each patient, mean glucose during admission was calculated from all glucose values measured during ICU admission. As markers for glucose variability, the MAG change[2] and the standard deviation were calculated per patient. Hypoglycaemia was defined as one or more glucose values ≤ 2.2 mmol/L, which is in accordance with previous trials.[7,11] Although our blood glucose target range in the initial years was between 4.0 and 7.0 mmol/L, we later found an association between the presence of a glucose value ≤ 4.7 mmol/L and ICU mortality.[3] Low glucose was therefore defined as the presence of at least one glucose value between 2.3 and 4.7 mmol/L.

Statistical analyses

Continuous data are presented as mean (standard deviation) or median (interquartile range), as appropriate, and compared using Student's t test or the Mann-Whitney rank-sum test, respectively. Categorical data are presented as percentages and compared using the chi-square test. In accordance with our previous studies, mean glucose and glucose variability (MAG change) were categorised into equally sized quintiles[14] and quartiles[2] and were plotted against ICU mortality for the DM and non-DM cohorts separately. The independent association between mean glucose and ICU mortality was examined using multivariable logistic regression analysis calculating odds ratios (ORs) with 95% confidence intervals (CIs). The quintile with the lowest mortality incidence was used as a reference. Based on clinical relevance and prognostic scoring, we adjusted for demographics (age, sex), severity of disease (using the APACHEII score), hypoglycaemia (≤ 2.2 mmol/L) and cardiothoracic surgery as the admission category. Cardiothoracic surgery was included as a covariate for several reasons: a generally lower mortality in this group compared with other surgical patients, a relatively low APACHE II score, a relatively short length of ICU stay and several different demographic and physiological characteristics of this group from the general ICU population, which could be reflected in differences in mean glucose concentration and glucose variability.[29] In an alternative model, adjustment was made for the occurrence of glucose values ≤ 4.7 mmol/L, which is also independently associated with mortality.[3,30] A second multivariable regression model was used to assess the independent association between glucose variability (MAG change) and ICU mortality, the quartile with lowest mortality incidence used as a reference. In this model the same potential confounders were used including the variable mean glucose. Furthermore, to assess the association between hypoglycaemia (≤ 2.2 mmol/L) and low glucose (2.3 to 4.7 mmol/L) and ICU mortality, unadjusted and adjusted ORs with 95% CIs were calculated, the latter using a third multivariable regression model adjusted for age, sex, severity of disease, cardiothoracic surgery and sepsis as admission diagnoses.

In both cohorts, we also assessed the cut-off value for detrimental low glucose, by performing the latter analysis for different blood glucose cut-off values. Additionally, when we adjusted the logistic regression models for the change in target glucose range in the studied period, no change in our results was observed (data not shown). All statistical analyses were performed in SPSS 18.0 (SPSS Inc, Chicago, IL, USA).

Results

From 11,901 ICU admissions, 10,320 patients were selected for analyses after excluding 842 readmissions, 105 patients with a withholding care policy, and 714 patients with < 3 glucose measurements. The remaining cohort consisted of 8,682 (84.2%) patients who did not have DM at the time of ICU admission (non-DM cohort) and 1,638 (15.8%) patients who had DM at the time of ICU admission (DM cohort). The percentage of medical and surgical ICU admissions in the entire cohort was 26% and 74%. The non-DM:DM ratio within these groups was 9:1 in patients with a medical ICU admission diagnosis and 4:1 in patients with a surgical ICU admission diagnosis. Table 1 illustrates patient characteristics of the entire study population as well as the differences between the non-DM cohort and the DM cohort.

3 *Association between mean glucose concentration and ICU mortality*

Figure 1 demonstrates the quintiles of mean glucose ranges per cohort (non-DM cohort: < 6.8, 6.8 to 7.3, 7.3 to 7.9, 7.9 to 8.9, > 8.9 mmol/L; DM cohort: < 6.9, 6.9 to 7.4, 7.4 to 8.0, 8.0 to 8.9, > 8.9 mmol/L) and corresponding ICU mortality rates. This resulted in a U-shaped relationship between mean glucose and ICU mortality in the non-DM cohort, with high ICU mortality in the lowest and highest glucose quintile (11.8% and 7.7%). Multivariable logistic regression analysis in the non-DM cohort showed that mean glucose values in the lowest and highest quintiles were associated with a significantly higher OR for ICU mortality compared with the quintile with the lowest ICU mortality (Figure 2). This was supported by a significant nonlinear relationship between mean glucose and ICU mortality (P for trend < 0.001). When we adjusted the logistic regression model for the occurrence of glucose values ≤ 4.7 mmol/L, the OR for ICU mortality in the lowest quintile no longer reached significance in the non-DM cohort (OR = 1.3, 95% CI = 0.9 to 1.8, P = 0.17). The increased ICU mortality in the non-DM cohort in the lower part of the U-curve therefore seems to be due to the relation between glucose values ≤ 4.7 mmol/L and ICU mortality. In contrast, no clear pattern was found in the DM cohort in unadjusted (Figure 1B) or multivariate analysis (data not shown).

Table 1 Characteristics, glucose and treatment variables for patients without/with diabetes mellitus and the total cohort

	No Diabetes (n=8,682)	Diabetes (n=1,638)	*P*-value[a]	Total cohort (n=10,320)
Age (years)	65 ± 13	68 ± 10	< 0.001	65 ± 13
Male sex	5,804 (67)	1,032 (63)	0.003	6,836 (66)
Body mass index (kg/m²)	27 ± 14	29 ± 5	< 0.001	27 ± 13
APACHE II score on admission	16 [13-21]	16 [13-20]	0.006	16 [13-21]
Maximum SOFA score during admission[b]	6 [5-8]	6 [5-7]	0.09	6 [5-8]
ICU stay, (hours)	26 [20-66]	23 [19-49]	< 0.001	25 [20-64]
Died in the ICU	622 (7)	73 (5)	< 0.001	695 (7)
Died in the hospital	994 (11)	144 (9)	0.001	1,138 (11)
Medical admissions	2,444 (28)	266 (16)	< 0.001	2,710 (26)
Surgical admissions	6,238 (72)	1,372 (84)	< 0.001	7,610 (74)
Cardiothoracic surgery patients	4,877 (56)	1,214 (74)	< 0.001	6,091 (59)
APACHE II admission category				
Cardiovascular	5,776 (67)	1,338 (82)	< 0.001	7,114 (69)
Sepsis	628 (7)	93 (6)	0.02	721 (7)
After cardiac arrest	534 (6)	37 (2)	< 0.001	571 (6)
Gastro-intestinal	474 (5)	43 (3)	< 0.001	517 (5)
Haematological	18 (0)	1 (0)	0.205	19 (0)
Renal	60 (1)	9 (1)	0.519	69 (1)
Metabolic	81(1)	14 (1)	0.761	95 (1)
Neurological	266 (3)	12 (1)	< 0.001	278 (3)
Respiratory	845 (10)	91 (6)	< 0.001	936 (9)
Glucose values per patient	12 [7-27]	14 [11-28]	< 0.001	13 [8-28]
Mean absolute glucose change (mmol/L/hr)	0.6 [0.4-0.8]	0.8 [0.6-1.0]	< 0.001	0.7 [0.4-0.9]
Standard deviation (mmol/L)	1.7 [1.3-2.3]	2.1 [1.6-2.7]	< 0.001	1.8 [1.4-2.4]
Incidence hypoglycaemia ≤ 2.2 mmol/L[c]	310 (4)	57 (4)	0.856	367 (4)
Incidence glucose value 2.3-4.7 mmol/L[c]	3,715 (43)	901 (55)	< 0.001	4,616 (45)

Table 1 (continued).

	No Diabetes (n=8,682)	Diabetes (n=1,638)	*P*-value[a]	Total cohort (n=10,320)
Use of insulin	6,686 (77)	1,610 (98)	< 0.001	8,296 (80)
Insulin dose (IU/hour)	2.2 [1.7-3.1]	2.8 [2.0-4.0]	< 0.001	2.3 [1.8-3.3]
Use of vasopressor drugs	8,020 (92)	1,551 (95)	0.001	9571 (93)
Use of corticosteroids	8,561 (99)	1,636 (100)	< 0.001	10,197 (99)
Mechanical ventilation[d]	8,039 (93)	1,539 (94)	0.050	9,578 (93)
Continuous veno-venous haemofiltration	690 (8)	116 (7)	0.231	806 (8)

Data presented as mean ± standard deviation, n (%) or median (interquartile range). APACHE, Acute Physiology and Chronic Health Evaluation; SOFA, Sequential Organ Failure Assessment. [a]Based on Student's t test or the Mann-Whitney rank-sum test (continuous data), or the chi-square test (categorical data), comparing patients with and without diabetes. [b]Maximum score during admission, calculated from the total individual scores calculated each ICU day. [c]Patients who experienced at least one hypoglycaemia or glucose value between 2.3 and 4.7 mmol/L. [d]In the first 24 hours of ICU admission.

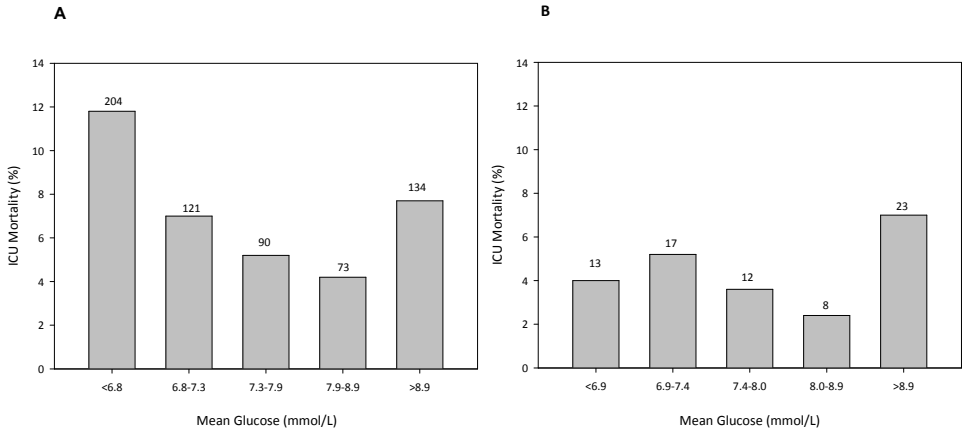


Figure 1. ICU mortality per quintile of mean glucose in the nondiabetes mellitus and diabetes mellitus cohorts. ICU mortality (%) per quintile of mean glucose in **(A)** the nondiabetes mellitus cohort and **(B)** the diabetes mellitus cohort. Numbers above bars indicate the number of deaths per mean glucose quintile.

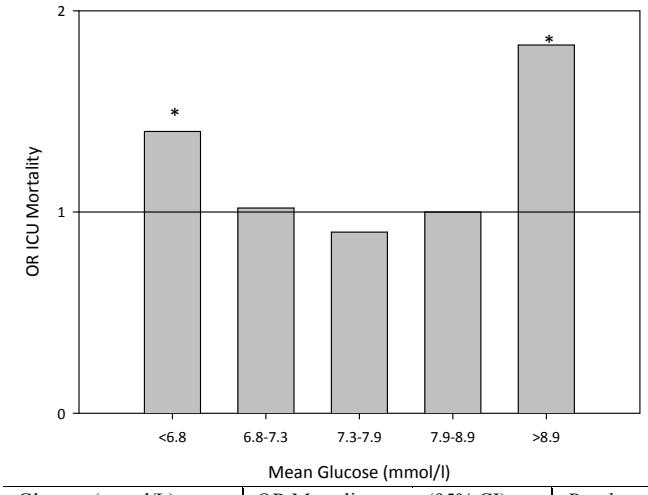
Association between hypoglycaemia and low glucose and ICU mortality

The percentage of patients who experienced at least one episode of hypoglycaemia (≤ 2.2 mmol/L) was similar in both cohorts (Table 1). Low glucose (2.3 to 4.7 mmol/L) occurred more frequently in the DM cohort. The increase in glucose target range as introduced in 2009 decreased the percentage of patients who experienced both hypoglycaemia (before 3.3%; after 0.3%) and low glucose (before 36.3%; after 8.4%). ICU mortality rates for hypoglycaemia were 29.7% and 21.1% in the non-DM and DM cohorts, respectively.

Association between glucose variability and ICU mortality

The ranges of MAG change per quartile (non-DM cohort: < 0.37, 0.37 to 0.56, 0.56 to 0.82, > 0.82 mmol/L/hour; DM cohort: < 0.56, 0.56 to 0.76, 0.76 to 1.03, > 1.03 mmol/L/hour) and corresponding ICU mortality per cohort are shown in Figure 3. This resulted in a linear relationship in the non-DM cohort, with the highest mortality rate seen in the upper MAG quartile (13.4%). Multivariable logistic regression analysis for the non- DM cohort is displayed in Figure 4; the OR for ICU mortality was highest in the upper MAG change quartile (OR = 1.69, P = 0.001). This was supported by a significant relationship between MAG quartiles and ICU mortality (P for trend = 0.004). In contrast, in the DM cohort no clear pattern was found in unadjusted (Figure 3B) or multivariate analysis (data not shown).

Unadjusted ORs of hypoglycaemia (≤ 2.2 mmol/L) for ICU mortality in the occurrence of hypoglycaemia were 6.2 (95% CI = 4.8 to 8.1, P < 0.001) in the non-DM cohort and 6.6 (95% CI = 3.3 to 13.1, P < 0.001) in the DM cohort. In logistic regression analysis, adjusted for potential confounders (see above), the OR of hypoglycaemia for ICU mortality was still significant in both cohorts (non-DM cohort: OR = 2.5, 95% CI = 1.8 to 3.4, P < 0.001; DM cohort: OR = 4.2, 95% CI = 1.8 to 10.1, P = 0.001).ICU mortality rates for low glucose (2.3 to 4.7 mmol/L) were 13.1% and 5.2% in the non-DM and DM cohorts, respectively. The OR of low glucose for ICU mortality was significant in the non-DM cohort (unadjusted OR = 5.3, 95% CI = 4.4 to 6.4, P < 0.001; adjusted OR = 1.5, 95% CI = 1.2 to 1.9, P < 0.001). When exploring the cutoff value for detrimental low glucose in the non-DM cohort, we found that lowest blood glucose concentrations up to 4.9 mmol/L were associated with an increased risk for ICU mortality (adjusted OR = 1.3, 95% CI = 1.1 to 1.7, P = 0.01). In contrast, when exploring the cutoff value for detrimental low glucose in the DM cohort, we found that lowest blood glucose concentrations up to 3.5 mmol/L were associated with an increased risk of ICU mortality (adjusted OR = 2.1, 95% CI = 1.2 to 3.7, P = 0.01). With glucose values between 3.5 and 4.7 mmol/L, no significant effect on the OR for ICU mortality was found. Poisson regression analysis, which we used in a previous study to adjust for daily Sequential Organ Failure Assessment score over time [3], amounted to similar results (data not shown).



Glucose (mmol/L)	OR Mortality	(95% CI)	*P-value*
< 6.8	1.40	(1.0 – 2.0)	0.04
6.8-7.3	1.02	(0.7 – 1.4)	0.90
7.3-7.9	0.90	(0.6 – 1.3)	0.55
7.9-8.9	Reference		n.a.
> 8.9	1.83	(1.3 – 2.6)	< 0.001

P for trend: 0.001

Figure 2. Odds ratio for ICU mortality per quintile of mean glucose in the nondiabetes mellitus cohort.
All odds ratios (ORs) were calculated per quintile of mean glucose and adjusted for age, sex, Acute Physiology and Chronic Health Evaluation II admission score, cardiothoracic surgery as admission diagnosis and the occurrence of hypoglycaemia (≤ 2.2 mmol/L). *P < 0.05. CI, confidence interval.

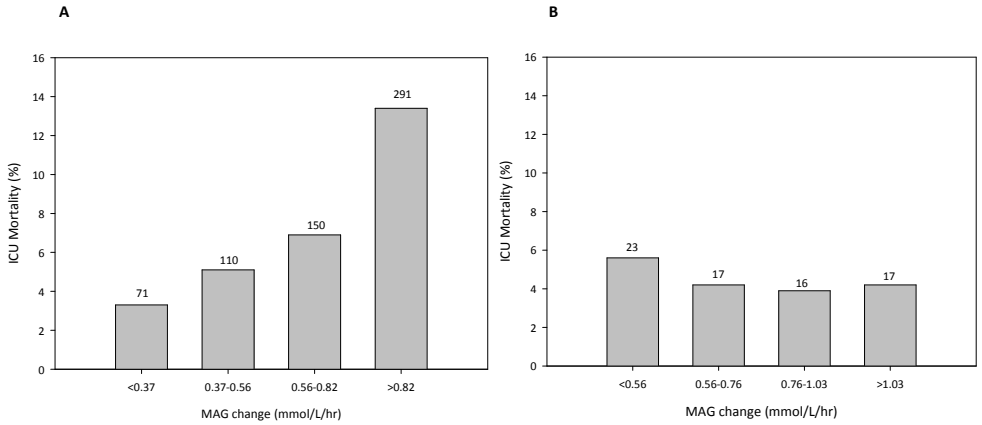
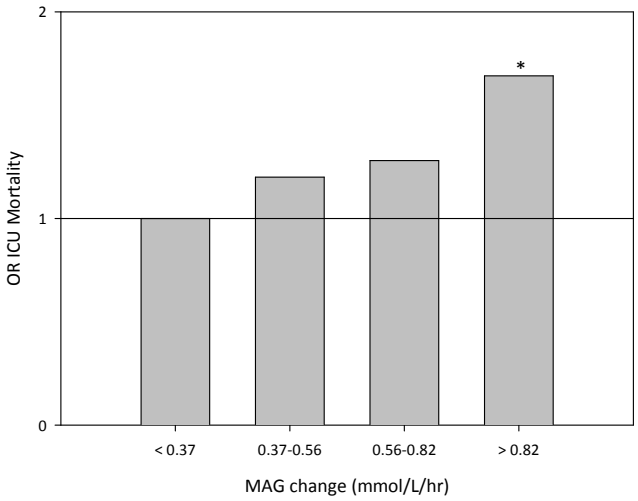


Figure 3. ICU mortality per mean absolute glucose change quartile in non-diabetes mellitus and diabetes mellitus cohorts. ICU mortality (%) per mean absolute glucose change (MAG) quartile in **(A)** the nondiabetes mellitus cohort and **(B)** the diabetes mellitus cohort. Numbers above bars indicate number of deaths per mean absolute glucose change quartile.



MAG change (mmol/L/hr)	OR Mortality	(95% CI)	*P-value*
< 0.37	Reference		n.a
0.37-0.56	1.20	(0.9-1.7)	0.29
0.56-0.82	1.28	(0.9-1.7)	0.13
> 0.82	1.69	(1.2-2.3)	0.001

P for trend =0.004

Figure 4.Odds ratio for ICU mortality over mean absolute glucose quartiles in the nondiabetes mellitus cohort. All odds ratios (ORs) were calculated per quartile of mean absolute glucose (MAG) change and adjusted for age, sex, Acute Physiology and Chronic Health Evaluation II admission score, mean glucose, cardiothoracic surgery as admission diagnosis and the occurrence of hypoglycaemia (≤ 2.2 mmol/L). **P* < 0.05. CI, confidence interval.

Discussion

In this retrospective database cohort study evaluating the association of four measures of glycaemic control and ICU mortality concomitantly, we found striking differences between the non-DM cohort and the DM cohort. In the non-DM cohort, ICU mortality was significantly related to all four measures of glycaemic control: mean glucose, glucose variability, the occurrence of hypoglycaemia (≤ 2.2 mmol/L) and low glucose concentrations up to 4.9 mmol/L. In contrast, in the DM cohort, only the occurrence of hypoglycaemia (≤ 2.2 mmol/L) and low-glucose concentrations up to 3.5 mmol/L were significantly associated with ICU mortality, while mean glucose and glucose variability were not. The presence of DM thus seems to affect the association between glucose control and ICU mortality.

Our findings support the results of previous studies that have focused on understanding the association between the presence of DM at ICU admission, glycaemia, and ICU mortality.[7,8,16–19,31,32] In all these studies, a stronger association between hyperglycaemia and ICU mortality was found in patients without DM, in comparison with patients with DM. Hypoglycaemia has been found to be a risk factor of mortality in patients without and with DM in the literature.[3,4,7,8,30,33,34] Of note, different cut-off values were used to define hypoglycaemia, ranging from ≤ 2.2 mmol/L[4,35] up to ≤ 4.7 mmol/L.[3,33] We also found a significant independent association between hypoglycaemia (≤ 2.2 mmol/L) and ICU mortality, in both the non-DM and DM cohorts. However, the association between low glucose (2.3 and 4.7 mmol/L) and ICU mortality was only significant in the non-DM cohort, not in the DM cohort. When exploring the cut-off value for detrimental low glucose in the present cohort, we found that lowest blood glucose concentrations up to 4.9 mmol/L were associated with an increased risk of ICU mortality in the non-DM cohort, and 3.5 mmol/L in the DM cohort. The cut-off value in the non-DM cohort is in line with our previous study, in which we found that lowest glucose values up to 4.7 mmol/L were associated with significant increased ICU mortality.[3] Furthermore, this cut-off value is supported by the finding that the higher mortality in the lower half of the U-shaped curve (< 6.8 mmol/L) in the non-DM cohort is mainly determined by the occurrence of glucose values ≤ 4.7 mmol/L and less by the glucose range between 4.7 and 6.8 mmol/L. The cut-off value for detrimental low glucose we found in our DM cohort (≤ 3.5 mmol/L) is also in line with the literature.[23,30] Both studies found that glucose concentrations ≤ 3.9 mmol/L were significantly associated with mortality in a subgroup of DM patients. Altogether, we can conclude that the cut-off value for detrimental low glucose is lower in the DM population than in the non-DM population.

The association between glucose variability and ICU mortality in patients without and with DM was studied previously.[22] In this observational study of 4,084 patients (including 942

DM patients), a strong association of glucose variability—expressed as the coefficient of variation (standard deviation/mean glucose level)—with mortality was found in patients without DM, while, in concordance with our study, no association was found in patients with DM.[22] Of note, this measure of glucose variability does not take order and time into account.

Several explanations can be considered for the different associations between glycaemic control and ICU mortality in patients without and with pre-existing DM. We previously suggested that adaptation to hyperglycaemia might be a key mechanism.[15] Acute hyperglycaemia and inflammation induce oxidative stress, which causes endothelial damage.[36] In patients without DM, cellular adaptation mechanisms will be activated for the first time in the acute care setting, whereas patients with DM could already have adapted to these insults during their years with DM and therefore better tolerate episodes of hyperglycaemia in an acute care setting. In addition, cellular adaptation to recurrent hypoglycaemia is also a well-established phenomenon.[37–39] Although speculative, adaptation to low glucose will already be present in patients with DM and might explain why patients with DM can withstand relatively low glucose values better.

Our results should be viewed in light of the study's strengths and limitations. Strengths of our study include the large number of ICU patients and that glucose values were captured automatically, which prevents transcription errors. Furthermore, this is the first study examining all four markers of glycaemic control in a non-DM cohort and a DM cohort simultaneously. Also, we used a time-based metric for glucose variability and we explored multiple cut-off values for hypoglycaemia.

Potential limitations of the study are that it is a single-centre study and retrospective in design, and thus is potentially subject to systematic error and bias. However, all data were prospectively collected and independently measured. Moreover, the findings are robust and internally consistent.

As in all studies in this field, our definition for a patient's diabetic status may be nonrepresentative. Unfortunately, glycosylated haemoglobin testing was not performed before ICU admission and we were unable to make a distinction between type 1 and type 2 DM patients. In addition, we were not able to distinguish between diabetes patients with good and poor chronic control, who may become hyperglycaemic due to acute illness. Whether this might affect the optimal glucose target for the DM cohort remains unknown.

Another limitation was that we were not able to distinguish between spontaneous (illness-related) and treatment-induced hypoglycaemia or variability. However, other studies could make this distinction. Finfer and colleagues reported that patients who had encountered severe or moderate hypoglycaemia while not being treated with insulin were at an increased mortality risk.[23] But they also demonstrated that, although to a lesser extent, insulin-induced hypoglycaemia was associated with an increased risk for ICU death. In contrast, Kosiborod and colleagues only reported a high risk for mortality in patients hospitalised with acute myocardial infarction who developed hypoglycaemia spontaneously. Iatrogenic hypoglycaemia after insulin therapy was not associated with higher mortality risk.[40]

Furthermore, in our cohort, most patients were admitted for cardiothoracic surgery; we corrected for this potential confounder in our regression analyses and still found significantly increased ICU mortality in the lowest and highest mean glucose quintiles and in the highest glucose variability quartile in the non-DM cohort. Moreover, the high amount of cardiothoracic surgery patients in the studied cohort may also have contributed to the high administration level of corticosteroids. In our hospital, as in many European hospitals (but not in most North American cardiac surgical centres), corticosteroid administration during cardiac surgery is part of routine care. All patients who were in shock or had sepsis or systemic inflammatory response syndrome also received corticosteroids. This could possibly limit the external validity of this single-centre study.

In our analyses of glucose variability, we did not correct for the frequency of glucose measurements during ICU admission. However, we did correct for severity of disease, which in itself is clearly correlated with the frequency of glucose measurements and ICU mortality. Furthermore, the concern that the frequency of blood glucose measurements may influence the relation between the MAG and ICU mortality has been previously discussed.[41] MAG is independent of the number of measurements, as long as blood glucose keeps changing at a constant rate. The MAG only increases when there is actually more glucose variability. The possibility to capture variability, if there is any, increases when the number of glucose measurements is increased. However, this can be said for all measures of glucose variability and this is not unique for the MAG change.

A limitation of our correction for severity of disease is the use of the APACHE II score. Although the validation of the use of APACHE II score to predict mortality in cardiac surgery patients is lacking, this adjustment is the best available method.[29]

Finally, because of the observational nature of the study, no proof of causation can be derived from the abovementioned associations between glycaemic control and ICU mortality.

Conclusion

This retrospective database cohort study shows that the presence of DM affects the association between three out of four measures of glycaemic control and ICU mortality. Mean glucose and high glucose variability were associated with ICU mortality in the non-DM cohort but not in the DM cohort, whereas hypoglycaemia (≤ 2.2 mmol/L) was associated with ICU mortality in both. We additionally found a higher cutoff value for detrimental low glucose in our non-DM cohort (4.9 mmol/L) than the DM cohort (3.5 mmol/L). Glucose concentrations ≤ 4.9 mmol/L should therefore be avoided in the non-DM cohort, while DM patients seem to tolerate a wider glucose range. Further studies should examine whether new technologies - that is, continuous glucose monitoring technology - could be of use for clinicians to improve glycaemic control.

Key messages

- The presence of DM affects the association between three out of four measures of glycaemic control and ICU mortality.
- Mean glucose relates to ICU mortality by a U-shaped curve in the non-DM population, whereas no clear association was found in the DM population.
- High glucose variability is only related to ICU mortality in the non-DM cohort.
- The occurrence of hypoglycaemia (≤ 2.2 mmol/L) is related to ICU mortality in both populations and should undoubtedly be avoided.
- The cut-off value for detrimental low glucose in the non-DM population (4.9 mmol/L) seems to be higher than in the DM population (3.5 mmol/L).

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4

Higher glucose variability in type 1 than type 2 diabetes patients admitted to the intensive care unit

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Submitted

Abstract

Background

Although the course of disease of type 1 and type 2 diabetes patients differs, the distinction between the specific type of diabetes is rarely made when patients are admitted to the intensive care unit (ICU). Here we report patient- and admission-related characteristics in relation to glycaemic measures of type 1 and type 2 diabetes patients admitted to the ICU.

Materials and Methods

A retrospective chart review was performed. A total of 1574 patients with diabetes admitted between 2004 and 2011 to the 24-bed mixed surgical and medical ICU of the Onze Lieve Vrouwe Gasthuis were included. Glycaemic measures included mean glucose both at and during admission, the incidence of hypo- and hyperglycaemia, percentage of glucose values in-, below- and above target, and glucose variability. ICU- and hospital mortality were secondary outcomes.

Results

We classified 2% (n = 27) of patients as having type 1 diabetes and 98% (n = 1547) as type 2 diabetes. Type 1 diabetes patients were significantly younger, had a lower BMI and were more frequently admitted to the ICU for medical diagnoses. No differences in glycaemic measures were found between the two cohorts, apart from glucose variability being 20% higher in the type 1 diabetes group.

Conclusion

A high glucose variability was found in type 1 diabetes patients, but overall glycaemic control was not different between type 1 and type 2 diabetes patients. Very few diabetes patients admitted to the ICU have type 1 diabetes.

Introduction

The optimal blood glucose management of critically ill patients remains highly debated among critical care physicians. Increasing evidence shows that perhaps not one single glycaemic target 'fits' for all patients admitted to the intensive care unit (ICU).[1] Recently, two large observational studies have shown that the presence of diabetes affects the association between several measures of glycaemic control and mortality.[2,3] Specifically, in non-diabetic critically ill patients mean glucose, hypoglycaemia and glucose variability are associated with increased mortality, while among critically ill patients with diabetes only hypoglycaemia is associated with increased mortality.[2,3] As a result, it has been suggested that targets in patients with diabetes should be set higher, as avoidance of hypoglycaemia is even more important than in non-diabetic patients.[1-3]

Remarkably, the distinction between the specific type of diabetes (type 1 or type 2 diabetes) has not been made in the major investigations with regard to glycaemic control and mortality and is often mentioned as a study limitation.[2-4] If at all, diabetes patients are classified according to treatment (oral-, insulin-therapy or diet only, or insulin-treated and non-insulin treated diabetes mellitus). Using these classifications, type 1 diabetes patients will still be 'mixed' with type 2 diabetes patients. This may lead to inaccurate interpretations with regard to glycaemic control in the ICU.

In this report, we classified patients with diabetes as type 1 or type 2 and we describe patient- and admission-related characteristics in relation to glycaemic measures of type 1 and type 2 diabetes patients admitted to the ICU.

Methods and Materials

A retrospective chart review was performed on the existing cohort of patients with diabetes (n=1638) admitted to the 24-bed medical/surgical ICU at the Onze Lieve Vrouwe Gasthuis, Amsterdam between 2004 and 201.[3] According to national guidelines this research is exempt from ethical approval because of its retrospective character.

Glucose regulation protocol

All patients were treated according to a standard blood glucose regulation protocol, which was targeted to achieve glucose values of 4.0-7.0 mmol/L from 2004-2009 and 5.0-9.0 mmol/L from April 2009 until 2011. Insulin adjustments were advised using a fully computerized sliding scale algorithm which is connected to the clinical information system.[5] Glucose was measured from blood samples obtained from an arterial catheter using the Accu-chek glucose meter (Roche/Hitachi, Basel, Switzerland).

Data collection

Baseline demographic variables, admission diagnoses and severity of disease score (Acute Physiology and Chronic Health Evaluation (APACHE II) were collected for all patients at ICU admission. Glucose values, insulin doses, medication- and nutrition data and mortality rates were extracted from patient records. Available glycosylated hemoglobin levels (within three months before ICU admission) were collected retrospectively from patient medical records.

To make a distinction between type 1 and type 2 diabetes all available medical outpatient records and admission history were reviewed. Type 1 diabetes was defined on the basis of epidemiological data: treatment with insulin and a diagnosis at the age of 30 years or younger.[6] In addition, no oral glucose-lowering therapy was allowed to be classified as type 1 diabetes. The diagnosis type 1 diabetes was verified by a telephone call to the patient´s general practitioner.

Study outcomes

The primary end point of this analysis was glycaemic control during ICU admission. Glycaemic measures were: mean blood glucose, admission blood glucose, amount of glucose values, percentage of blood glucose measurements in-, above and below target range, hypoglycaemia (<2.2 mmol/L) and hyperglycaemia (>15.0 mmol/L), glucose variability (expressed as Mean Absolute Glucose (MAG) change and SD) , and insulin data. Secondary endpoints included ICU and hospital mortality, length of stay (LOS) at the ICU and ventilator days.

Statistical analysis

Continuous data are expressed as mean ± SD for normally distributed variables and median (interquartile range) for other variables. Categorical data are expressed as the number of subjects. Group comparisons are performed using the t test for normally distributed data and Mann-Whitney-U test for other continuous variables. Fisher's exact test was used for categorical variables. A p value < 0.05 was considered statistically significant. Statistical analyses were performed using IBM SPSS software 20.0 (SPSS Inc, Chicago, IL, USA).

Results

Of the 1638 charts reviewed, data from a total of 1574 patients were included in the analysis. Excluded were 55 (3%) readmissions, 4 (0.2%) patients with a diagnosis of type 3 diabetes (due to pancreas-related disorders) and 5 (0.2%) patients who erroneously had a diagnosis of diabetes. The remaining cohort consisted of 27 (2%) patients with type 1 diabetes and 1547 (98%) patients with type 2 diabetes. Table 1 summarizes demographic and admission-related characteristics of both cohorts. Compared to type 2 diabetes patients,

type 1 diabetes patients were significantly younger (age 57 ± 12 versus 68 ± 10 years; P <0.001) and had a lower BMI (24.6 ± 4 versus 28.7 ± 5 kg/m2; P < 0.001) at ICU admission. APACHE II score was similar in both cohorts. Medical admissions (admission categories sepsis and metabolic) occurred more frequently in type 1 diabetes patients (P = 0.004), whereas in type 2 diabetes patients surgical (cardiovascular) admissions were more common (P = 0.03). Two patients in the type 1 diabetes group were admitted for diabetic ketoacidosis. Furthermore, mechanical ventilation and the use of vasopressor drugs was more frequent in type 2 diabetes patients (P=0.04 and 0.003). Pre-admission glycosylated hemoglobin level was significantly higher in type 1 diabetes patients (P <0.01) although only a few pre-admission values were available for type 1 patients.

Table 1 Demographic and admission-related characteristics of the type 1 and type 2 diabetes cohort

	Type 1 diabetes patients (n=27)	**Type 2 diabetes patients (n=1547)**	***P*-value**
Age (years)	57 ± 12	68 ± 10	<0.001
Male sex	14 (52)	981 (64)	0.23
Body mass index (kg/m²)	24.6 ± 4	28.7 ± 5	<0.001
APACHE II score on admission	16 (12-18)	16 (13-20)	0.28
Medical admissions	10 (37)	231 (15)	0.004
Surgical admissions	17 (63)	1316 (85)	0.004
Cardiothoracic surgery patients	16 (59)	1181 (76)	0.07
APACHE II admission category			
Cardiovascular	18 (67)	1295 (84)	0.03
Sepsis	4 (15)	74 (5)	0.04
After cardiac arrest	0 (0)	34 (2)	1.0
Gastro-intestinal	0 (0)	37 (2)	1.0
Haematological	0 (0)	1 (0.1)	1.0
Renal	0 (0)	6 (0.4)	1.0
Metabolic	2 (7.4)	10 (0.6)	0.02
Neurological	1 (3.7)	10 (0.6)	0.17
Respiratory	2 (0.1)	80 (5.2)	0.65
Use of vasopressor drugs	23 (85)	1473 (95)	0.04
Use of corticosteroids	27 (100)	1544 (100)	1.0
Mechanical ventilation[a]	21 (78)	1466 (95)	0.003
Continuous veno-venous haemofiltration	3 (11)	99 (6)	0.25

Table 1 (continued).

	Type 1 diabetes patients (n=27)	Type 2 diabetes patients (n=1547)	*P*-value
Glucose lowering therapy at admission[b]			
Metformin	-	964 (63)	
Mean daily dose (mg)	-	1515 ± 730	
Insulin	27 (100)	572 (37)	<0.001
Mean daily dose (IU)	51 ± 19	64 ± 41	0.01
Sulfonylureas	-	602 (39)	
Thiazolidinediones	-	40 (2.6)	
Dipeptidyl Peptidase-4 inhibitors	-	5 (0.3)	
Combination tablets	-	11 (0.7)	
Other	-	8 (0.5)	
Unknown	-	53 (3.4)	
No DM medication	-	14 (0.9)	
Glycosylated hemoglobin level (%)[c]	9.7 (8.1-12.8)	7.3 (6.3-8.3)	0.01
Total parenteral nutrition	0 (0)	7 (0.5)	1.0
Enteral nutrition	8 (30)	410 (27)	0.67

Data presented as mean ± standard deviation, n (%) or median (interquartile range). APACHE: Acute Physiology and Chronic Health Evaluation; [a]In de first 24 hours of ICU admission, [b]Glucose lowering medication use at home, [c]Glycosylated hemoglobin level was collected in 240 patients (type 1 n=5; type 2 n = 235).

4 *Glycaemic Control*

Table 2 compares the glycaemic measures between type 1 and type 2 diabetes patients. Glucose variability expressed as the MAG change was almost 20% higher in type 1 diabetes patients (1.1 mmol/L/h in type 1 diabetes versus 0.9 mmol/L/h in type 2 diabetes; P = 0.01). All other glycaemic measures were similar in type 1 and type 2 diabetes patients.

Secondary Outcomes

The unadjusted ICU mortality rate was 3.7% in the type 1 diabetes group compared to 4.3% in the type 2 diabetes group (P = 1.0) as seen in table 2. Hospital mortality, LOS in the ICU and ventilator days also did not differ significantly between the two cohorts.

Table 2 Glycaemic control during ICU admission and secondary outcomes of the two cohorts

	Type 1 diabetes patients (n=27)	Type 2 diabetes patients (n=1547)	*P*-value
Glycaemic Measures			
Mean glucose (mmol/L)	8.3 ± 2.4	8.0 ± 1.6	0.42
Admission blood glucose (mmol/L)	12.5 ± 8.9	9.9 ± 3.7	0.14
Percentage of glucose values			
in target range[a]	50 ± 20	51 ± 19	0.78
below target range[a]	6 ± 11	4 ± 6	0.24
above target range[a]	44 ± 22	45 ± 20	0.72
Maximum glucose (mmol/L)	15 ± 9	13 ± 4	0.19
Minimum glucose (mmol/L)	4.5 ±1	4.7 ±2	0.42
Morning glucose (mmol/L)	8.0 ± 3.2	7.0 ± 2.0	0.15
Glucose values per patient	15 [11-29]	14 [11-27]	0.93
Incidence hypoglycaemia ≤ 2.2 mmol/L[b]	1 (3.7)	52 (3.4)	0.61
Incidence glucose value 2.3-4.7 mmol/L[c]	14 (52)	844 (55)	0.85
Incidence hyperglycaemia ≥ 15 mmol/L[d]	7 (26)	318 (21)	0.48
Mean absolute glucose change (mmol/L/hr)	1.1 [0.8-1.6]	0.9 [0.7-1.2]	0.01
Standard deviation (mmol/L)	2.4 [1.8-2.6]	2.1 [1.6-2.7]	0.41
Insulin dose (IU/hour)	2.3 [2.0-4.0]	2.8 [2.0-4.0]	0.34
Secondary outcomes			
ICU mortality	1 (3.7)	66 (4.3)	1.0
Hospital mortality	3 (11.1)	129 (8.3)	0.49
ICU stay, (days)	2.5 ± 4.8	2.5 ± 4.9	0.97
Ventilator days	2.0 ± 2	2.4 ± 4	0.63

Data presented as mean ± standard deviation, n (%) or median [interquartile range]. [a]Until 2009 glucose target of 4.0-7.0 mmol/L, after 2009 glucose target of 5.0-9.0 mmol/L. [b]Patients who experienced at least one hypoglycaemia, [c]Patients who experienced at least one glucose value between 2.3 and 4.7 mmol/L, [d]Patients who experienced at least one hyperglycaemia.

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Discussion

Around 15 to 20% of patients admitted to ICUs overall are estimated to be patients with diabetes.[7,8] These patients represent a unique population with regard to glycaemic control. To the best of our knowledge, this is the first report to specifically classify and compare type 1 and type 2 diabetes patients admitted to the ICU with regard to demographic and admission-related characteristics in relation to glycaemic control. The results show a younger age, a lower BMI and more medical than (cardio)surgical ICU admissions in type 1 diabetes patients compared to type 2 diabetes patients, as could be expected. Glucose variability, expressed as the MAG change, was found to be higher in the type 1 diabetes group. No relevant differences were found in the other glycaemic measures between the two cohorts.

As the World Health Organization states that type 2 diabetes compromises 90% of people with diabetes around the world,[9] the initial hypothesis was that we would find some 10 percent of patients with type 1 diabetes in our ICU diabetes cohort. Contrary to our expectations, only a small number of type 1 diabetes patients (n=27 or 2%) was identified in our cohort. Four studies also reported the proportion of type 1 diabetes in diabetes patients admitted to the ICU, which ranged from 5 to 12.4%.[4,7,10,11] All four studies did not mention how type 1 diabetes was classified. Moreover, to make a distinction in type of diabetes was not their primary goal. Perhaps, type 1 diabetes was used to denote insulin-treated diabetes, thus, misclassification might be possible and might explain the difference in proportion of type 1 diabetes compared to our study, along with the differences in ICU population. The overall lower age of the type 1 population seems a likely explanation for the lower than expected prevalence of the disease in the ICU.

Glucose variability was the only glycaemic measure that differed between type 1 and type 2 diabetes patients. This is in line with the observation that type 1 diabetes patients show higher glucose variability compared to type 2 diabetes patients in an outpatient setting. Unfortunately, whether type 1 diabetes impacts the relation between glucose variability and ICU mortality could not be investigated. The level of endogenous insulin production, the level of insulin resistance during critical illness and the counter-regulatory responses may be different in type 1 and type 2 diabetes patients and might explain why glucose variability differs between the groups.

A similar APACHE II score was found between type 1 and type 2 diabetes patients. It should be noted that age is one of the incorporated variables in the APACHE II score. The younger age of type 1 diabetes patients in our cohort implies that type 1 diabetes patients score higher at other physiological and laboratory variables of the APACHE II. This

suggests that type 1 diabetes patients may have been more severely ill than type 2 diabetes patients, when taking their younger age into account.

The difference in age between type 1 and type 2 diabetes, the pre-admission glucose regulation as well as the variety in diseases to which patients are admitted to an ICU could possibly affect the relation between glycaemic control and mortality. Unfortunately, the small sample size of type 1 diabetes patients hampered us to analyze the relationship between glycaemic measures and ICU mortality in the studied cohorts using multivariate models and is a major study limitation. Whether type of diabetes impacts the association between glycaemic measures and ICU mortality needs to be investigated in a larger group of type 1 and type 2 diabetes patients.

Other limitations of this study include the retrospective and single-center design which may limit the generalizability of the results. Furthermore, although the epidemiological definition of type 1 diabetes has been previously validated,[6] misclassification in diabetes type remains possible. Data of islet cell-specific autoantibodies (glutamic acid decarboxylase 65 and the tyrosine phosphatase-related islet antigen 2), which give a combined sensitivity for type 1 diabetes of up to 98%,[12] was not available in the majority of our type 1 diabetes patients. Lastly, pre-admission glycated haemoglobin level was available in a minority of the patients only. Nevertheless, we found similar glycated haemoglobin levels compared to a previous study that reported a mean glycated haemoglobin level of 7.5% (58 mmol/mol) in 360 diabetes patients.[13] This suggests that the majority of patients with diabetes, regardless of diabetes type, have suboptimal glycaemic control prior to their acute illness.

Conclusion

Although modest differences in demographic- and admission-related characteristics exist between patients with type 1 and type 2 diabetes admitted to the ICU, glycaemic control was similar, apart from glucose variability which was found higher in type 1 diabetes patients. Overall, the proportion of type 1 diabetes at the intensive care unit was low.

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Insulin treatment guided by subcutaneous continuous glucose monitoring compared to frequent point-of-care measurement in critically ill patients: a randomized controlled trial

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Critical Care 2014 Aug 20;18(4):453

Abstract

Background

Glucose measurement in intensive care medicine is performed intermittently with the risk of undetected hypoglycaemia. The workload for the ICU nursing staff is substantial. Subcutaneous continuous glucose monitoring (CGM) systems are available and may be able to solve some of these issues in critically ill patients.

Materials and Methods

In a randomized controlled design in a mixed ICU in a teaching hospital we compared the use of subcutaneous CGM with frequent point-of-care (POC) to guide insulin treatment. Adult critically ill patients with an expected stay of more than 24 hours and in need of insulin therapy were included. All patients received subcutaneous CGM. CGM data were blinded in the control group, whereas in the intervention group these data were used to feed a computerized glucose regulation algorithm. The same algorithm was used in the control group fed by intermittent POC glucose measurements. Safety was assessed with the incidence of severe hypoglycaemia (<2.2 mmol/L), efficacy with the percentage time in target range (5.0 to 9.0 mmol/L). In addition we assessed nursing workload and costs.

Results

In this study, 87 patients were randomized to the intervention and 90 to the control group. CGM device failure resulted in 78 and 78 patients for analysis. The incidence of severe hypoglycaemia and percentage of time within target range was similar in both groups. A significant reduction in daily nursing workload for glucose control was found in the intervention group (17 versus 36 minutes; P <0.001). Mean daily costs per patient were significantly reduced with EUR 12 (95% CI −32 to −18, P = 0.02) in the intervention group.

Conclusion

Subcutaneous CGM to guide insulin treatment in critically ill patients is as safe and effective as intermittent point-of-care measurements and reduces nursing workload and daily costs. A new algorithm designed for frequent measurements may lead to improved performance and should precede clinical implementation.

Clinicaltrials.gov, NCT01526044. Registered 1 February 2012.

Introduction

Stress induced hyperglycaemia is common and relates to adverse outcomes in critically ill patients.[1,2] The outcomes of two large intervention studies are in some way contradictory but the consensus is that hyperglycaemia should be corrected, while avoiding hypoglycaemia and high glucose variability.[3–8] On the basis of the available evidence it seems preferableto maintain a blood glucose level around 8.0 mmol/L for the majority of critically ill patients.[9,10] Glucose regulation regimens require frequent monitoring of glucose, which leads to a considerable workload for the intensive care (IC) nurses. In addition, glucose regulation carries an inherent risk of insulin-induced hypoglycaemia, which is associated with mortality.[6] Information about the glucose level is lacking for the period in-between measurements with possible unnoticed hypoglycaemic episodes. Continuous glucose monitoring (CGM) could be of value to facilitate or improve glycaemic control. Previous studies have indicated an acceptable accuracy and reliability for subcutaneous CGM devices in critically ill patients.[11–15] The only prospective randomized controlled trial so far which assessed the role for CGM in glycaemic control in critically ill patients showed that real-time CGM increased the safety of tight glycaemic control in critically ill patients by significantly reducing severe hypoglycaemic events.[16] However, an improvement of the mean glucose concentration by using real-time CGM was not found.[16] Thus, CGM may give us the ability to detect early (possible) hypo- and hyperglycaemia as well as minimizing swings in glucose levels. Moreover, the use of CGM may facilitate the process of glycaemic control and may reduce the number of blood samples and accompanying blood loss, nursing workload and costs. To date, there are few data available how CGM-driven glucose regulation compares to point-of-care driven glucose regulation and no controlled studies specifically evaluated workload and cost of CGM. The aim of the present study was to assess the safety, efficacy, workload and costs of a subcutaneous CGM system guided blood glucose regulation in comparison with frequent point-of-care blood glucose guided regulation in a mixed population of critically ill patients.

Material and methods

Study design and participants

This was a randomized controlled open label clinical trial, performed in a 20-bed mixed medical-surgical ICU of a teaching hospital (Onze Lieve Vrouwe Gasthuis, Amsterdam, the Netherlands). Patients were recruited over a period of 18 months from 2011 till late 2012. Patients were eligible for inclusion within 24 hours after ICU admission if they were 18 years or older, in need of intravenous (i.v.) insulin treatment for glucose

regulation and with an expected length of stay in the ICU of at least 24 hours. Patients could not be included if any of the following criteria was present: lack of informed consent, participation in another trial or previous participation in this trial or when a CGM system was currently not available. The study ended when patients were discharged from the ICU or because of technical failure of the CGM device. The maximum study duration was set at 5 days for both treatment groups. The complete nursing staff was trained beforehand to handle all devices used in this study adequately. This study was approved by the ethics committee VCMO, Nieuwegein, The Netherlands and was in line with Dutch and European legislation. All patients or their legal representative provided written informed consent. This trial is registered with Clinicaltrials.gov, number NCT01526044.

Randomisation

Patients who met the inclusion criteria were randomised in a 1:1 ratio with computerised block randomisation to either the intervention group or the control group.

Study procedures

Algorithm

In all study participants, blood glucose regulation was performed by a sliding scale algorithm with a blood glucose target of 5.0 to 9.0 mmol/L, which was integrated into the patient data management system (PDMS, MetaVision; *i*MD*soft*, Tel Aviv, Israel).[17] Hypoglycaemia was defined as a blood glucose level of <2.2 mmol/L in line with the Van den Berghe trial.[3] Below target was defined as a glucose level from 2.2 mmol/L till the lower target level of 5.0 mmol/L. Above target were all glucose levels above 9.0 mmol/L. The algorithm instructed the insulin i.v. infusion rate (or glucose administration in case of hypoglycaemia) after each glucose measurement. The time for the next glucose measurement was also defined from the algorithm and was depended on the stability of the glucose level over time.

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Glucose measurements

Study participants allocated to the intervention group received a subcutaneous CGM system (FreeStyle Navigator®, Abbott Diabetes Care, Alameda, CA, USA), which was used to guide blood glucose regulation. The nurses were trained to insert the subcutaneous glucose sensors on the patients' abdomen or upper arm. After insertion of the subcutaneous sensor, a transmitter was attached which connects through wireless communication to a receiver, which displays the real-time glucose readings every minute and stores glucose readings every 10th minute. The CGM system needed a one-hour stabilization period, in which glucose measurements were not performed. Calibration of the system using an arterial blood sample was performed 5 times in total, after 1, 2, 8–10, 24–32 and 72–80 hours, following manufacturer instructions. The CGM system alarmed when additional calibrations were needed. On the times that the algorithm needed a new glucose

measurement, the readings from the CGM system were entered in the computerized glucose regulation protocol that was embedded in the PDMS. Other CGM values were not used in the algorithm. The CGM system alarmed when the glucose level was either <5.0 mmol/L or >9.0 mmol/L. When this occurred, the nurse entered this additional glucose level in the computerized protocol, which triggered the glucose algorithm to advise an insulin dosing adjustment. The CGM repeated its alarm when after 15 minutes the glucose level was still out of target range. Again, this value was entered into the system and dose adjustments were made until target range was achieved.

Every hypoglycaemic event (<2.2 mmol/L) needed to be verified by an arterial blood glucose sample. In case of a discrepancy between the CGM value and the arterial blood glucose sample, the latter was leading in clinical decision-making. Blood glucose regulation in the study participants allocated to the control group was performed by use of frequent point-of-care (POC) measurements using Accu-Chek® (Roche/Hitachi, Basel, Switzerland). All blood samples were obtained from an indwelling arterial catheter. The displayed glucose levels were automatically stored in the PDMS. Participants in the control group also received a subcutaneous Freestyle Navigator CGM system, however, these data were blinded and not used for blood glucose regulation. Calibrations were performed following manufacturer instructions and no alarms were set. In both groups arterial reference blood glucose samples were drawn six times daily at standardized times and analyzed by the ABL Flex automated blood gas analyzer (BGA) (Radiometer, Copenhagen, Denmark). These values were automatically stored into the PDMS but were blinded to both nurses and physicians.

Study endpoints

The primary safety outcome was the incidence of severe hypoglycaemia (<2.2 mmol/L) during the intervention. Efficacy outcomes were the percentage of time that glucose levels were within the target range (5.0-9.0 mmol/L), below target range (2.2–5.0 mmol/L), and in the hyperglycaemic range (>9.0 mmol/L). In addition, mean blood- and sensor glucose levels and glucose variability defined as the mean absolute glucose (MAG) change (ΔGlucose/ΔTime) were endpoints too.[8] The accuracy of the CGM- and the point-of-care (POC) device was assessed by calculating the median relative absolute deviation (RAD) between reference glucose and CGM- or POC glucose.

Nursing workload for glucose control per day was determined by the number of POC measurements or measurements from the sensor which were entered in the computerized glucose regulation protocol and the amount of calibrations of the CGM sensor (intervention group only). A time-in-motion design was used to estimate the time that it took to execute targeted glucose control and insulin treatment per group. The following subtasks were observed: (1) POC measurement (this included the initiation, blood sampling, blood testing

and processing), (2) sensor placement, (3) sensor calibration and (4) time needed to determine a CGM value and entering the value in the decision support module. The tenfold recorded elapsed times per subtask were averaged and then multiplied by the 24-hour blood sample average collected from the clinical trial.

Cost analysis was performed from a health care payer perspective with a 1-day (24 hours) time horizon. The outcome measure in the economic evaluation was the costs per patient for glycaemic control in 24 hours. Cost parameters included nursing personnel costs, device costs, materials needed for glucose monitoring and laboratory costs. Cost estimates for the parameters were derived from the hospital- and laboratory ledger, devices manufacturers' data and the Dutch guide for health-economic research.[18] Costs are expressed in euros and are based on the year 2013. Because of the short time horizon of this analysis (24 hour), the costs were not discounted.

Data collection

Clinical and laboratory baseline data were extracted from the PDMS after randomisation: demographic data, body mass index (BMI), reason for ICU admission, history of diabetes, history of renal failure, severity of disease scores (the sequential organ failure assessment (SOFA) score and Acute Physiology and Chronic Health Evaluation (APACHE IV) score at admission), blood glucose levels at admission and the use of mechanical ventilation.

Blood glucose data, i.e. reference arterial blood glucose samples and glucose values that were entered in the decision support module (CGM measurements in the intervention group, POC measurements in the control group) were also extracted from the PDMS. Continuous glucose data from the CGM device were uploaded to a computer using CoPilot® Health Management System for FreeStyle Navigator (Abbott Diabetes Care, Alameda, CA, USA) and entered in the study database. All reference glucose measurements were linked by time with the concomitant CGM measurements and Accu-Chek measurements.

Statistical analysis

A sample size of 160 (80 participants in each group) conferred 80% power, with two sided $p = 0.05$, to detect an absolute difference of 10% in the incidence of severe hypo- or hyperglycaemia between the intervention and the control group. A total sample size of 178 patients (89 patients per group) is needed to correct for an expected 10% drop out. Results are expressed as percentages for categorical variables, mean and standard deviation (SD) for continuous normally distributed variables, and median and interquartile

range (IQR) for continuous non-normally distributed variables. Groups were compared by using Fisher's Exact test, Student's *t* test or Mann Whitney rank-sum test were appropriate. Median RAD was calculated instead of mean because of its skewed distribution.

Costs were calculated as the summed product of factors and resources used and their respective unit costs and were averaged per patient per day. Because of skewed (cost) distributions, we assessed group contrasts by calculating 95% confidence intervals for the mean differences following bias corrected and accelerated nonparametric bootstrapping, i.e. drawing 1,000 samples of the same size as the original sample separately for each group. All statistical analyses were performed in SPSS 20.0 (SPSS Inc, Chicago, IL, USA).

Results

A total of 178 patients were randomized to either the intervention or the control group (Figure 1). Most of the patients who were not eligible were postoperative cardiac surgery patients with an expected length of stay (LOS) <24 hours. One patient was incorrectly randomized and did not receive a CGM device. Nine patients in the intervention group and twelve patients in the control group were excluded from analysis due to lack of CGM data because of technical failure of the device, being misplacement of the sensor (n = 3) and problems with extraction of the data (n = 18). We performed a per protocol analysis from the data of 78 patients in each group. Table 1 shows the two groups, which were well matched with respect to all baseline characteristics.

Treatment

During the intervention, a total of 37,570 (intervention group) and 32,957 (control group) CGM measurements were collected. The number of reference arterial blood gas glucose measurements was 1,599 in the intervention group and 1,325 in the control group. The median number of additional calibrations needed for the CGM was 1.9 per 24 hours (IQR 1.2-3.3]. The number of glucose values entered in the PDMS (CGM measurements in the intervention group and POC measurements in the control group) was 3,919 and 2,489 respectively.

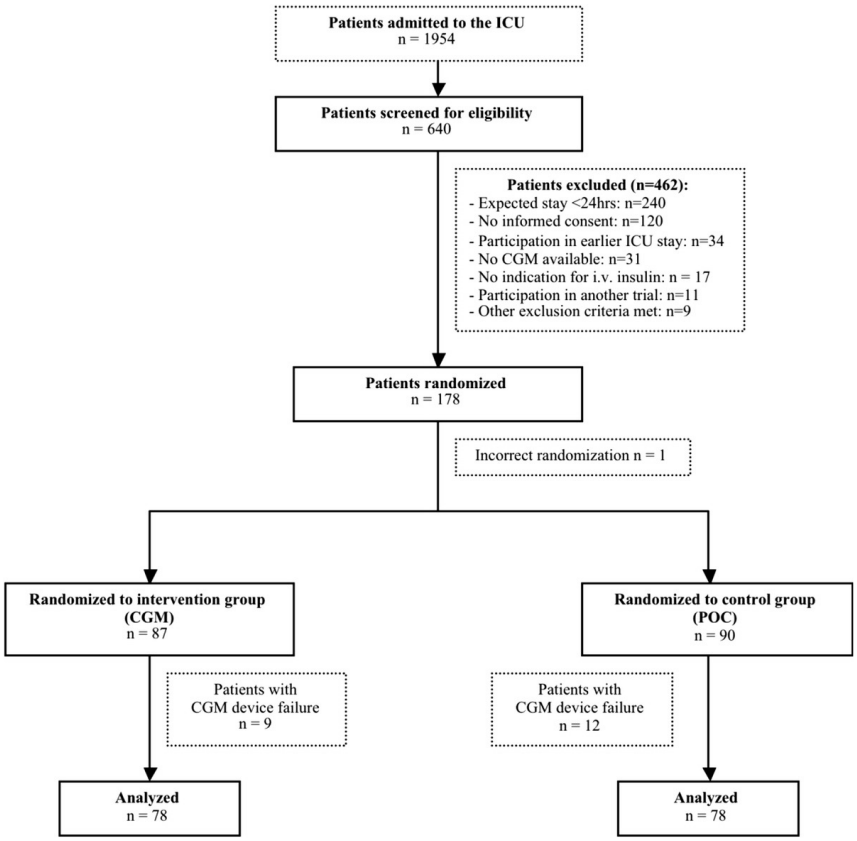

Figure 1 Flow chart of study participants; assessment, randomization and analysis.

Table 1. Baseline characteristics of participants

	Intervention – CGM (*n* = 87)	**Control – POCM** (*n* = 90)
Age (years)	66.4 (14.0)	67.2 (11.4)
Women	45 (52%)	35 (39%)
BMI (kg/m^2)	27.8 (7.0)	27.4 (5.8)
Weight (kg)	81.8 (21.7)	83.2 (21.5)
History of diabetes*	18 (21%)	21 (23%)
History of renal failure**	10 (12%)	5 (6%)
Reason for ICU admission		
Surgical		
Elective	19 (22%)	16 (18%)
Emergency	12 (14%)	13 (14%)
Medical	56 (64%)	61 (68%)
Admission diagnosis		
Post cardiac surgery	12 (14%)	11 (12%)
Severe sepsis / septic shock	23 (26%)	18 (20%)
Pneumonia	12 (14%)	11 (12%)
Cardiac failure	10 (12%)	9 (10%)
COPD	3 (3%)	8 (9%)
Hemorrhagic shock	7 (8%)	10 (11%)
Cardiac Arrest/resuscitation	10 (12%)	14(16%)
Other	10 (12%)	9 (10%)
APACHE IV predicted mortality (%)	32 (10–70)	31 (20–60)
SOFA score on admission	8 (6–10)	7 (6–10)
Blood glucose level on admission (mmol/L)	9.0 (2.6)	9.2 (2.5)
Mechanical ventilation	80 (92%)	83 (92%)

Data are mean (SD), median (IQR) or n (%). BMI: body mass index, ICU: intensive care unit, SOFA: sequential organ failure assessment, APACHE: acute physiology and chronic health evaluation, COPD: chronic obstructive pulmonary disease *Diabetes was defined as present when this diagnosis was mentioned in the medical history **Renal failure was present when the pre-admission serum creatinin was above 177umol/l.

Study outcomes

Table 2 summarizes the outcome measures of the study. The incidence of hypoglycaemia (<2.2 mmol/L), the primary safety endpoint, was similar in both the intervention and the control group. None of the severe hypoglycaemic episodes detected by the CGM in the intervention group was verified by arterial blood sampling. In the control group, all severe hypoglycaemic episodes detected by the CGM, occurred in-between two point-of-care glucose measurements and were not detected by the nurses. In total, there were 14 patients (3 patients in the control group and 11 patients in the intervention group) who experienced 19 "true" hypoglycaemic events (<3.9 mmol/L) detected by ABL. Twenty-five percent (n = 4) of the true "hypoglycaemic" events in the CGM group and 67% (n = 2) in the control group were also identified by CGM or POC (difference in glucose ≤ 10%). All other endpoints such as percentage time in target range, below target range, mean reference and sensor glucose, glucose variability, hospital length of stay, ICU and hospital mortality were non-significantly different between the study groups. Moderate hyperglycaemia (9.0-11.1 mmol/L) was significantly different in favor of the intervention group (p = 0.03).

A total of 355 time-linked reference glucose-CGM samples and 85 time-linked reference glucose-POC samples were used to assess accuracy of the devices. Median (IQR) RAD of the POC device was 7.1% (3– 12) whereas the median RAD of the CGM device was 13.7% (8–23) (p < 0.001). Bland-Altman plots per glucose monitoring system are shown in an additional file (Additional file 1: Figure S1).

Table 3 summarizes nursing workload data per 24 hour. The first column displays the average time burden per subtask of glucose control. The average total time burden for glucose control was significantly lower in the intervention group compared to the control group (17 minutes versus 36 minutes; p < 0.001). The mean reduction in total nursing workload was 19 minutes per 24 hour or 53% in favour of the intervention group. As in this study an open blood drawing system was used, 5 mL blood per POC measurement or calibration was taken from the patient. Blood loss was therefore significantly reduced in the intervention group (15.3 mL versus 60 mL per day; p < 0.001).

The economic analysis of both groups is shown in Table 4. The intervention group generated an average total daily cost of EUR 41, whereas the total daily cost in the control group was EUR 53. The difference in costs was EUR −12 in favor of the intervention group (95% CI −32 to −18, p = 0.02). The extra costs of the CGM devices in the intervention group were neutralized by the diminished costs for nursing personnel, material- and laboratory costs.

Table 2. Safety, efficacy and clinical study outcomes

	Intervention - CGM (*n* = 78)	**Control - POCM** (*n* = 78)	***P*-value**
Study period (days)	3.2 (2-5)	2.8 (1-5)	0.18
Incidence severe hypoglycaemia (<2.2 mmol/L)[1]	None	None	
Detected by CGM			
Number of subjects	3 (4%)	4 (5%)	1.0
Episodes < 2.2 mmol/L	3	4	
% of time for the reference glucose level (SD)[3]			
In target range (5.0-9.0 mmol/L)	69 (26)	66 (26)	0.47
Below target range (2.2-5.0 mmol/L)	5 (7)	3 (5)	0.21
Mild moderate hypoglycaemia (2.2-3.9)	1 (3)	0 (1)	0.03
Above target range (>9.0 mmol/L)	28 (26)	34 (27)	0.06
Mild moderate hyperglycaemia (9.0-11.1)	17 (16)	26 (23)	0.01
Hyperglycaemia (>11.1)	11(19)	7(14)	0.19
% of time for the sensor glucose levels (SD)[3]			
In target range (5.0-9.0 mmol/L)	75 (18)	71 (20)	0.18
Below target range (2.2-5.0 mmol/L)	11 (13)	9 (12)	0.44
Mild moderate hypoglycaemia (2.2-3.9)	2 (7)	1 (2)	0.14
Above target range (>9.0 mmol/L)	15 (16)	20 (21)	0.06
Mild moderate hyperglycaemia (9.0-11.1)	12 (11)	16 (16)	0.03
Hyperglycaemia (>11.1)	3 (7)	4 (9)	0.35
Mean reference blood glucose (mmol/L)	8.2 (1.6)	8.3 (1.3)	0.53
Mean sensor glucose (mmol/L)	7.1 (1.1)	7.5 (1.3)	0.07
MAG change (mmol/L/h)[2]	0.33 (0.2-0.5)	0.32(0.2-0.4)	0.31
LOS ICU (hours)	137 (71-250)	95 (51-157)	0.04
LOS hospital (days)	15 (8-270)	14 (8-31)	0.91
Mortality ICU	15 (19%)	12 (15%)	0.67
Mortality hospital	22 (28%)	17 (22%)	0.46

Data shown are mean (SD), median (IQR), or *n* (%). CGM: continuous glucose monitoring; MAG: mean absolute glucose change; LOS: length of stay; ICU: intensive care unit. [1]Patients who experienced at least one severe hypo- or hyperglycaemic episode, verified by blood gas analysis. [2]When at least three reference glucose measurements were available (intervention *n* = 73, control *n* = 71). [3]Percentages do not add up to 100 due to rounding off.

Table 3 Nursing workload per day (24 hours)

	Time per action (min)	Nr of actions in control group	Nursing time control group (min)	Nr of actions in intervention group	Nursing time intervention group (min)
POC measurement	3	12 (8)	36 (24)	0.06 (0.4)	0.2 (0.4)
Sensor CGM placement	3.5	-	-	1	3.5
Sensor CGM calibration	2.5	-	-	1.9 (1.2-3.3)	8 (11)
Sensor CGM data to enter in PDMS	0.3	-	-	18 (10)	5.3 (3)
Total time (min)			**36 (24)**		**17 (12)***

POC: point-of-care; CGM: continuous glucose monitoring; PDMS: patient data management system.
Data are expressed as mean (SD), or median (IQR)* $p < 0.001$ in comparison with control group.

Table 4 Cost analysis

	Costs per unit	Factor control group	Costs in control group	Factor intervention group	Costs in intervention group	Difference in costs (95% C.I.)[1]
Nursing time	€38/hr	36 min	€22.98	17 min	€10.87	€-12·11(-16, -9)
CGM receiver	€1009.59	-	-	€1.38 per day[2]	€1.38	€1.38
CGM Sensor	€61.00	-	-	€24.40 per day[3]	€24.40	€24.40
CGM calibration[4]	€1.19	-	-	3.3	€3.95	€3.95 (3,5)
Accu-Chek Inform II device	€892.37	€1.22 per day[2]	€1.22	-	-	€-1.22
Material POC measurement[5]	€0.70	12.2	€8.51	0.06	€0.04	€-8.47 (-10,-7)
Laboratory[6]	€1.66	12.2	€20.18	0.06	€0.10	€-20.08 (-23,-18)
Total costs			**€52.89**		**€40.74**	**€-12.42 (-22, -5)**

Factors and costs are expressed as means per patient per day (24-hour). CGM: continuous glucose monitoring, POC: point-of-care measurement.[1]95% confidence interval based on 1000 stratified bootstrap samples. [2]Assuming a lifetime of two years; [3]Assuming a manufacturers' sensor lifetime of two and a half days; [4]Calibration strip CGM; [5]Includes syringes, non-sterile gloves, gauzes, alcohol, cap (used for blood sampling) and testing strip POC. [6]Costs for a single point-of-care glucose measurement.

Discussion

The present study showed that a subcutaneous CGM system to guide blood glucose regulation was equally effective and safe in glycaemic control compared to frequent point-ofcare guided blood glucose regulation. However, CGM significantly reduces nursing workload, blood loss and the daily costs for glucose control.

Comparison with other studies

This is the second but largest randomized controlled trial in which CGM is used to guide glycaemic control in critically ill patients. In contrast to our findings, Holzinger and colleagues did find less severe hypoglycaemia in the CGM group.[16] This may be caused by the very low incidence of severe hypoglycaemia in the present study, which was true for both the intervention and the control group. This may be related to a change of policy after the publication of the NICE-SUGAR trial,[4] which was a reason for our and most other ICUs to increase their blood glucose target range. The increased target range may have reduced the incidence of hypoglycaemic events.[19,20] Indeed, the blood glucose target used in the current study (5.0-9.0 mmol/L) was higher than in the Holzinger trial[16] (4.4-6.1 mmol/L) and this is reflected in the achieved mean blood glucose levels (8.1 vs. 6.3 mmol/L). Moreover, the use of a fully computerized algorithm for glucose control and the high familiarity of the protocol among our IC nurses may have contributed to the low incidence of severe hypoglycaemia. The available studies to date on tight glucose control showed an increase in nursing workload.[21–23]

The potential benefits of CGM in the reduction of blood samples, blood loss and nursing workload was assumed in previous studies, but was not systematically assessed before. We now observed that CGM significantly reduced the amount of blood samples and the daily nursing workload for glucose control up to 53%. This finding seems clinically relevant, especially in a busy clinical IC environment.

Two studies focused on the cumulative nursing workload accompanied with tight glucose control protocols.[21,22] Gartemann et al. estimated that nurses devoted approximately 42 minutes during a 12-hour shift of their time to administering a TGC protocol, whereas Aragon et al. even reported that up to 2 hours might be required for tight glycaemic control for a single patient in a 24-hour period. In our POC control group, the mean nursing workload estimate was less (36 min per 24 hour) than the published estimates reported by other groups. This might partly be explained by the use of a fully computerized algorithm for glucose control in our ICU. In addition, the familiarity of the protocol is very high among our ICU nurses.

Effectiveness and costs

The use of CGM did not achieve improved glycaemic control in our study. We found similar percentages of time-in-target and below-target range between the study groups. The not significantly lower percentage of time in the hyperglycaemic range in the intervention group could be explained by the fact that CGM measurements were more frequently entered in the glucose protocol than POC measurements in the control group. This probably resulted in more adjustments in the insulin treatment with lower blood glucose levels as a consequence. The significantly increased ICU LOS, which was observed in the intervention group, may be a coincidence or reflect unmeasured case-mix factors but is in our view unrelated to the glucose measurement strategy.

In contrast to our expectations, the cost analysis shows that the use of CGM systems for glucose control in an ICU setting is not a priori an expense. However, we should be cautious in interpreting these results due to the rather short time-horizon (24 hour) in the analysis of costs determination and the single-centre study design. Also, cost savings cannot immediately be monetized due to the short time horizon used in this cost-analysis.

Accuracy of the subcutaneous measurements

The subcutaneous Freestyle Navigator CGM device that we used in the present study showed a median RAD of 13.7%, which is higher than 10.6 and 11.6% that was found in previous validation studies of this device in critically ill patients, suggesting an accuracy acceptable for clinical use.[11,14] The lag time that may be needed for the subcutaneous compartment to adapt to the intravenous compartment appeared not to be clinically relevant.[11] However, the accuracy as assessed in the current study seems to indicate a need for improvement, because the accuracy was less than the accuracy of the Accu-Chek and because a substantial number (75% in CGM group and 33% in control group) of hypoglycaemic events was not detected.

Interestingly, Leelarathna et al.[24] recently investigated whether there was a difference in accuracy of the Freestyle Navigator in a critical care setting using two methods of calibration: 1) calibration according to the manufacturer's instructions (1, 2, 10, and 24 h) or 2) calibration at variable intervals of 1-6 h using ABG. Using enhanced calibration, at a median (interquartile range) every 169 (122–213) min, the absolute relative deviation was lower (7.0% [3.5, 13.0] vs. 12.8% [6.3, 21.8], $P < 0.001$). So, further significant improvements in accuracy may be obtained by frequent calibrations with ABG measurements. In the current study forced calibration was not possible, calibration was only performed when the CGM device indicated the need for calibration by itself.

In addition, technical problems with the subcutaneous CGM device were observed during the study and led to a 12% dropout. The most important reason was the temporary loss of

sensor signal from several minutes to hours that resulted in a loss of data. Difficulties in the calibration process were also identified as the CGM could only be calibrated if the system indicated a calibration by itself, which occurred for median 1.9 times per 24 hours. Most of the technical difficulties however may have been due to lack of experience working with the CGM device despite the training of all ICU nurses. We expect such problems to be easily resolved with additional training and with the improved next generation Freestyle Navigator II, which has recently been introduced and showed good utility and sensor performance in critically ill patients.[25] This study aimed to define safety, efficacy and costs and therefore we neglected the system dropout at this moment. It is true, however, that this device can only become part of routine care when the dropout percentage diminishes.

Strengths and weaknesses

Strengths of our study include the relatively large sample size, the randomised controlled study design and the wide variety in case mix. However, some limitations of the present study merit further consideration.

First, the study was performed in a single Dutch intensive care unit, which limits the generalizability of the study. Second, the study was designed to blind the values of the CGM in the control group. However, the CGM needed to be calibrated several times during the study period, which made it impossible to blind it completely. Third, the nursing staff did not verify the severe hypoglycaemia that was indicated by CGM in two of the three patients despite specific instructions to do so. One of these two patients had evolved into a 'withholding care policy', which was the reason to accept the severe hypoglycaemia. We assume that in the other patient priority was given to other important nursing tasks. Thus, the available data are insufficient to define the accuracy of the CGM in the hypoglycaemic range. In our previous studies this was not identified as a clinical problem.[11,14] Also, with an adapted algorithm, the CGM should be able to detect a decreasing glucose level before hypoglycaemia is present and give a timely alert. Fourth, the computerized algorithm was designed for intermittent point-of-care measurements and not for (semi-) continuous data. As such, the patients did not fully benefit from the frequent glucose measurements by CGM. An algorithm based on ten-minute glucose input might have led to other results. We did identify this issue beforehand but we decided to keep the algorithm for both groups the same to be able to investigate the contribution of CGM per se. It can be expected that an adapted algorithm will further improve the performance of CGM in the guidance of glycaemic control.

Conclusions

Subcutaneous continuous glucose monitoring (CGM) to guide blood glucose regulation in critically ill patients was shown to be safe in terms of hypoglycaemia incidence. With an identical insulin treatment algorithm, the CGM performed equally effective as POC measurement. A new algorithm designed for frequent measurements may further improve the results and should precede clinical implementation. CGM significantly reduced nursing workload, blood loss and the daily costs for glucose control.

Key messages

- Insulin treatment based on continuous subcutaneous glucose monitoring (CGM) revealed the same number of hypoglycaemic events compared to point of care (POC)
- Subcutaneous CGM was equally effective as POC measured as glucose time in target range
- Total costs were lower when using subcutaneous CGM than frequent POC
- Nursing workload with glucose regulation was reduced by subcutaneous CGM compared to frequent POC
- A new algorithm designed for continuous measurement should be developed before CGM can be implemented clinically

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Acknowledgments

We express our gratefulness to the medical, nursing and ICT staff from the OLVG intensive care unit. The authors own department funded this study. Abbott did not fund this study in any way.

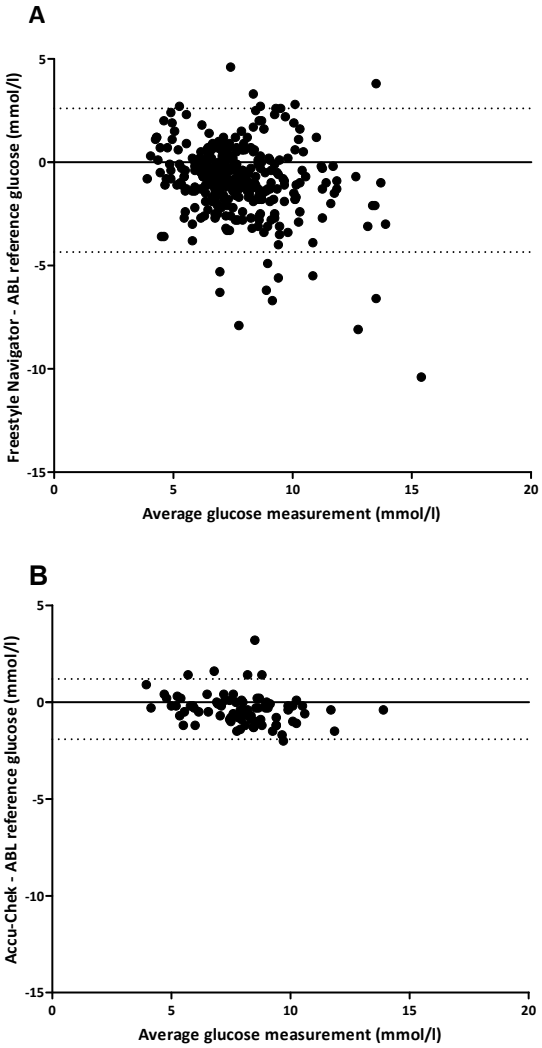

Figure S1 Bland-Altman plots per glucose monitoring system.
(A) CGM system (Freestyle Navigator) (B) Point of care measurement (Accu-Chek). The x-axis represents the average of sensor or device and reference glucose values in mmol/L. The y-axis represents the absolute difference between sensor or device and reference glucose values in mmol/L. The dotted lines represent the 5th and 95th percentile

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6

Accuracy of intra-arterial and subcutaneous continuous glucose monitoring in post-operative cardiac surgery patients in the ICU

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Journal of Diabetes Science and Technology 2014 Dec 23; 1–5

Abstract

Background

The GluCath® intra-arterial continuous glucose monitoring (IA-CGM) system uses a novel quenched chemical fluorescence sensing mechanism to optically measure blood glucose when deployed in the radial artery. The aim of this study was to compare the accuracy of the IA-CGM and the Freestyle Navigator® subcutaneous continuous glucose monitoring (SC-CGM) system with standard care.

Methods and materials

After admission to the intensive care unit (ICU), the IA-CGM was inserted via a 20 gauge radial arterial study catheter and the SC-CGM was placed at the abdominal wall of post-operative cardiac surgery patients with an expected ICU length of stay of > 24 hours. Each device was calibrated according to manufacturer instructions. Glucose values of both CGM systems were blinded for the clinical staff. Reference blood glucose samples were collected from the study catheter every 1–2 hours for at least 24 hours and analyzed on a Radiometer ABL Blood Gas Analyzer.

Results

6 The IA-CGM and SC-CGM sensors were successfully inserted in eight subjects. Accuracy assessment was performed with 183 paired points: 85.8% of the IA-CGM measurements and 84.2% of the SC-CGM measurements met ISO 15197:2003 glucometer criteria (within 20%) across a 79–248 mg/dl (4.4–13.8 mmol/L) glucose range. Overall ± SD mean absolute relative difference was 12.3 ± 11.3% for IA-CGM and 11.1 ± 8.3% for SC-CGM (difference -1.2%, 95% CI -3.3 to 0.8; $P = 0.24$).

Conclusion

The IA-CGM system directly measured arterial blood glucose and did not interfere with clinical care. However, accuracy was similar to that of the less invasive SC-CGM device.

Introduction

Glucose regulation is a key patient management goal in intensive care medicine and glycaemic control using intravenous insulin is thus widely practiced in intensive care units (ICUs)[1]. Currently, blood glucose concentration is almost universally measured intermittently using either point-of-care glucose meters or blood gas analyzers.[2] However, intermittent glucose measurement has several limitations. It does not provide data very frequently, which could result in missed episodes of hyper- and hypoglycaemia. Moreover, it is time-consuming for the ICU nursing staff.[3] Real time continuous glucose monitoring (CGM) devices in the ICU have the potential to address these limitations.

Several commercially available subcutaneous CGM systems have been tested in critically ill patients.[3-6] Most studies have shown an acceptable correlation between arterial and interstitial glucose using a subcutaneous CGM device, whereas some studies have reported suboptimal accuracy results.[7,8] The unpredictable subcutaneous conditions of intensive care patients is often regarded as a factor which may influence the measurement of glucose concentrations in the interstitial fluid. However, recent data indicate that impairment in microcirculation in cardiac surgery patients was not related to sensor accuracy.[9]

Theoretically, intra-arterial positioning of CGM devices could yield frequent, immediate and accurate glucose readings. Arterial access is frequently obtained in ICU patients and would be convenient to also use for continuous glucose monitoring. Here we report accuracy results of two CGM devices, the GluCath® intra-arterial continuous glucose monitoring (IA-CGM) system and the FreeStyle Navigator® subcutaneous continuous glucose monitoring (SC-CGM) system, in post-cardiac surgery patients admitted to the ICU.

Methods

Design and setting

This investigator-initiated sub-study with a head-to-head comparison to a SC-CGM was part of a larger open-label product development study to assess the safety and performance of the GluCath IA-CGM in an intended number of 20 ICU patients (including a cohort of 5 run-in patients). Subjects above the age of 18, scheduled for elective cardiothoracic surgery and who were admitted after surgery to the 24-bed medical/surgical ICU in the Onze Lieve Vrouwe Gasthuis (OLVG, Amsterdam, the Netherlands) were enrolled. Exclusion criteria were an expected ICU stay of < 24 hours, known pregnancy, known contraindication to heparin (present on the coating of the IA-CGM) and a known contraindication for adequate placement of the subcutaneous glucose device. The patients were studied during

ICU admission for at least 24 hours and up to a maximum of 48 hours. This study was approved by the ethics committees of the Academic Medical Center and Onze Lieve Vrouwe Gasthuis in Amsterdam in conformation with Dutch and European legislation. All patients or their legal representative provided written informed consent.

Glucose sensing of CGM devices

The GluCath IA-CGM (GluMetrics, Irvine, CA, USA) consists of a heparin-bonded sensor, which is deployed intravascularly approximately 2 cm beyond an arterial catheter. The novel quenched chemical fluorescence sensing mechanism of the GluCath IA-CGM has previously been described.[10,11] In brief, blue light travels down an optical fiber to the sensing chemistry at the distal tip of the sensor, which fluoresces green in proportion to the glucose concentration of the blood. It also measures and corrects for pH and blood temperature. Optical signals are processed in the monitor where the fluorescence intensity is converted to a prospectively calibrated glucose value, which is recorded every ten seconds. The Freestyle Navigator SC-CGM (Abbott Diabetes Care, Alameda, CA, USA) consists of an electrochemical sensor placed in the subcutaneous adipose tissue and measures glucose using a glucose oxidase method. Glucose readings of the Freestyle Navigator SC-CGM are displayed every minute.

Intervention

After admission to the ICU, two different sensors were inserted in each patient. The GluCath IA-CGM device (GluMetrics, Irvine, CA, USA) was inserted through a newly placed Arrow RA-4020 radial arterial catheter (Teleflex, Limerick, PA, USA) and attached directly to the hub of the arterial access of the catheter. Calibration of the IA-CGM was performed one and two hours after insertion and each subsequent study day at noon. The Freestyle Navigator SC-CGM device (Abbott Diabetes Care, Alameda, CA, USA) was inserted in the abdominal wall by a positioning system and continuously measured blood glucose after a one-hour warm-up period and calibration was performed according to manufacturers' instructions (at 1, 2, 10 and 24 hours after insertion, using a FreeStyle test strip and arterial blood specimen). The outputs of both sensors were masked to the investigators and clinical staff and no clinical decisions were made based on the output of the CGM systems. Ultrasound images were taken of the radial artery prior to IA-CGM insertion, after sensor insertion, and prior to removal. Both sensors were removed after a maximum of 48 hours of CGM or earlier if deemed clinically necessary or when the patient was discharged from the ICU. Glycaemic control to a blood glucose target of 90 to 162 mg/dl (5.0 to 9.0 mmol/L) was performed according to a sliding scale algorithm integrated into the patient data management system (PDMS, MetaVision; *i*MD*soft*, Tel Aviv, Israel).[12]

Data collection

Arterial reference blood glucose samples were obtained every hour during the day and every other hour during the night and were measured on a blood gas analyzer (Radiometer ABL 800 series, Radiometer Medical ApS, Brønshøj, Denmark). The IA-CGM measured glucose every ten seconds and recorded optical signals, temperature and prospectively-calibrated glucose values, whereas the SC-CGM displayed glucose readings every minute and stored the glucose value every tenth minute. Reference blood draw times were recorded on both the IA-CGM device and in the patient data management system. The IA-CGM value immediately prior to blood draw and a linear interpolation of the stored SC-CGM glucose values was paired with each reference value. In addition, since optimal accuracy of the Freestyle SC-CGM is reached 5-10 minutes after the reference glucose[6], sensor values of the SC-CGM 5-10 minutes after the reference glucose were also used to assess accuracy.

Statistical analysis

Accuracy outcome measures included mean absolute relative deviation (MARD) (the average % difference between sensor glucose values and reference values), median absolute relative difference (ARD), and Bland-Altman analysis. We additionally assessed accuracy criteria according to the ISO certification criteria for point-of-care glucometers (ISO 15197:2003) and accuracy criteria of Clinical Laboratory Standard Institute standard POCT12-A3. All analyses were performed using Excel (Microsoft, Redmond, WA, USA) and SPSS 20.0 (IBM, Armonk, NY, USA).

Results

Both IA-CGM and SC-CGM were successfully inserted in eight patients (three females and five male, median age 70 years (range 54 to 84). All patients underwent cardiothoracic surgery; coronary artery bypass graft (CABG) (n = 2), valve replacement (n = 4), CABG and valve replacement (n =1) or CABG and Bentall surgery (n = 1). Two patients were previously diagnosed with diabetes mellitus, median (IQR) APACHE IV and EUROSCORE predicted mortality were 2.4% (0.6–6.2) and 5.3% (3.3–6.9). Mean glucose (SD) during the intervention was 159 (27) mg/dl (or 8.8 (1.5) mmol/L).

All IA-CGM sensors functioned after the initial in vivo calibration. The devices continuously monitored blood glucose levels for a mean (SD) of 33 (9) hours. No sensors were removed or replaced as a result of device malfunctions. Two sensors were removed due to loss of arterial catheter patency (after 44 and 37 hours of monitoring); the remaining sensors were removed prior to discharge from the ICU or impending non study-related death (one patient). There were no device-related serious adverse events. No sensor interfered with clinical care, haemodynamic monitoring or blood sampling. The loss of

arterial catheter patency was due to failure to maintain flush solution in one subject and due to non-occlusive, subclinical thrombus that formed around the catheter after the other subject underwent an emergency thoracotomy. No treatment was required.

The SC-CGM device continuously monitored blood glucose levels during a mean (SD) of 29 (10) hours. In three patients a new SC-CGM device was placed due to failure of calibration (in two patients) or accidental removal during re-thoracotomy (one patient).

A total of 183 paired points were available for performance analysis of the two CGM devices. Paired reference glucose values ranged from 79 to 248 mg/dl (4.4–13.8 mmol/L). The MARD ± SD was 12.3 ± 11.3% for the IA-CGM and 11.1 ± 8.3% for the SC-CGM (difference -1.2%, 95% CI -3.3 to 0.8; P = 0.24). Individual IA-CGM sensors exhibited MARD from 8.4% to 17.5%. Individual SC-CGM sensors exhibited MARD from 5.3% to 16.0%.

Detailed accuracy data of the two sensors are shown in table 1. Accuracy of the SC-CGM slightly improved when using sensor values 5-10 minutes after the reference glucose value (i.e. taking into account the time-delay of subcutaneous measuring of glucose): overall MARD 10.8 ± 8.7%; overall median ARD: 8.8 (4-15)%. P-values for overall MARD and median ARD between the two devices (IA-CGM and delayed SC-CGM measurements) changed in 0.15 and 0.44 respectively. Furthermore, the SC-CGM performed slightly better 'in target' compared to 'above target' (MARD in target 10.1% and MARD above target 12.9%; P=0.04), whereas the IA-CGM performed equal across the two ranges.

Figure 1 shows Bland-Altman analysis and resulted in a similar mean bias (or systematic error) of -8.0 to -8.6 mg/dl for both sensors. The upper and lower limit of agreement was 39.4 and -56.5 mg/dl for the GluCath IA-CGM and 33.8 and -49.7 mg/dl for the Freestyle Navigator SC-CGM. There was no consistency in direction of error and no visual trend was observed for more inaccuracy approaching the hypo- or hyperglycaemic ranges. The figure also shows paired points meeting the accuracy criteria of the International Organization for Standardization standard 15197:2003. The ISO 15197: 2003 criteria (within 20% of reference when ≥ 75 mg/dl) were met in 157/183 (85.8 %) of the IA-CGM measurements and in 154/183 (84.2%) of the SC-CGM measurements (P = 0.77). Accuracy criteria of Clinical Laboratory Standard Institute standard POCT12-A3 (within 12.5% of reference when ≥ 101 mg/dl) were met in 113 / 183 (55.4%) of the IA-CGM measurements and in 120 / 183 (64.2%) of the SC-CGM measurements. Fourteen percent (26/183) of the paired points of the GluCath IA-CGM and 16% (29/183) of the paired points of the Freestyle SC-CGM differed > 20% of the reference analyzer glucose values.

Table 1 Accuracy data of the GluCath intra-arterial CGM system and the Freestyle subcutaneous CGM system

	GluCath IA-CGM	Freestyle SC-CGM	P-value
Number of CGM-reference pairs (n)	183	183	
Number of reference values between 'in target range' (90-162 mg/dl) (n)	106	106	
Number of CGM-reference pairs 'below target range' (<90 mg/dl) (n)[1]	5	5	
Number of CGM-reference pairs 'above target' (>162 mg/dl) (n)	72	72	
Overall MARD ± SD (%)	12.3 ± 11.3	11.1 ± 8.3	0.24
MARD 90-162 mg/dl ± SD (%)	12.4 ± 11.8	10.1 ± 7.6	0.10
MARD > 162 mg/dl ± SD (%)	11.8 ± 10.9	12.9 ± 9.1	0.50
Overall Median ARD (IQR) (%)	9.9 (4-16)	9.4 (5-15)	0.81
Median ARD 90-162 mg/dl (IQR) (%)	9.0 (4-16)	8.4 (5-13)	0.40
Median ARD > 162 mg/dl (IQR) (%)	9.3 (4-16)	12.3 (5-20)	0.19

CGM: continuous glucose monitoring; MARD: mean absolute relative difference; ARD: absolute relative difference; SD: standard deviation; IQR: interquartile range. [1]Number of hypoglycaemic measurements is too low to calculate accuracy data of the hypoglycaemic range.

DISCUSSION

This is the first report in literature in which accuracy results are shown of two CGM devices in the same ICU patient which differed in positioning and type of glucose measuring. We show similar accuracy with an MARD of 11–12% for both the GluCath IA-CGM and the Freestyle Navigator SC-CGM compared to arterial reference blood glucose samples in post-cardiac surgery patients admitted to the ICU.

Our accuracy results for the Freestyle Navigator are in line with our previous validation studies of this device in a small number of critically ill patients.[6,13] We recently investigated the use of the Freestyle Navigator CGM system to guide blood glucose regulation in a larger group of critically ill patients (n=178).[3] Accuracy of the Freestyle Navigator in this study was lower with an MARD of 17.1%. Improvements in accuracy of the Freestyle Navigator device may be obtained by performing calibrations more frequently.[14]

Another open-label study investigated the use of the GluCath IA-CGM device in cardiac surgery patients admitted to the ICU and reported similar accuracy with an aggregate MARD of 13.0% (individual sensors ranging from 4.7% to 33.5%).[15] As in all studies in this field, the extent of acceptable deviation between sensor and arterial reference glucose measurements can be debated. Recently, Finfer et al. stated in a consensus paper on the measurement of blood glucose in critically ill adults that a desirable point accuracy of CGM systems in critically ill patients is that 98% of glucose readings are within 12.5% of a reference standard and that the remaining 2% of readings should be within 20% of a

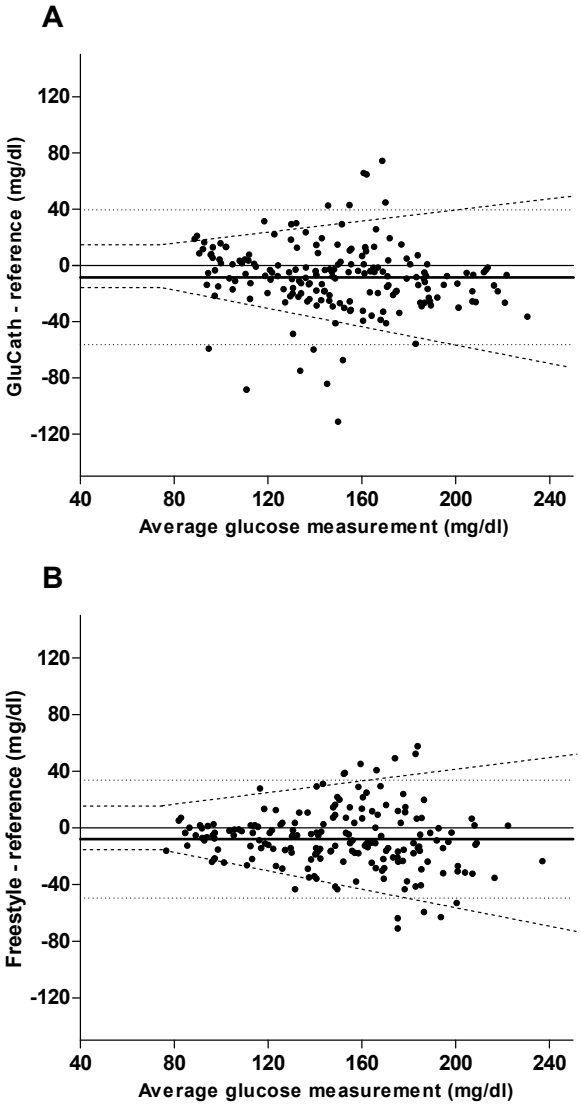

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Figure 1 ISO-Modified Bland-Altman plots for the **(A)** GluCath IA-CGM system and **(B)** Freestyle SC-CGM system. The x-axis represents the average of sensor and reference glucose measurements in mg/dl. The y-axis represents the absolute difference between sensor and reference glucose measurements in mg/dl. The solid line represents the mean difference (GluCath -8.6 and Freestyle -8.0 mg/dl); dotted lines are drawn at the mean difference±1.96 times the standard deviation of the mean difference. The long dashed lines represent the ISO-15197: 2003 criteria.

reference standard.[2] Unfortunately, the current data have not met these performance standards. For most CGM systems assessed in an intensive care setting, larger studies are needed to demonstrate sufficient accuracy in a broad range of critical care settings.

Our study has several limitations. This study was performed in a small number of subjects in a single population, elective post-cardiac surgical subjects, who are relatively-healthy compared to other ICU subjects that may benefit from CGM. In addition, we only measured glucose up to 48 hours and cannot comment on the performance of the devices beyond that point. Finally, we did only obtain glucose levels between 79 and 248 mg/dl and not in the hypoglycaemic range.

The GluCath IA-CGM system used in this study was an investigational device used as part of a manufacturer-sponsored product development study. While the system did not interfere with routine care by clinical staff once inserted, the IA-CGM device required a lengthy setup and on-patient securement by study staff. Poor IA-CGM system performance (> 11% MARD) in 3 subjects was attributed by the manufacturer to optical signal variability associated with routine patient care activities (e.g., receiving personal care, transitions from bed to chair, transport to OR), sub-optimal securement and the administration of 3 interfering medications (mannitol, citrate, glubionate). They did not correspond to clinical conditions of the patient. The company did not obtain funding to further develop their device and has since closed shop.

Reasons for poor SC-CGM system performance was not studied extensively in the current study. One subject was in a cardiogenic shock, which was a complication of an aortic – and mitral valve replacement surgery. The subject underwent an emergency thoracotomy. Interestingly, accuracy of the SC-CGM system in this specific subject was good, with an individual MARD of 5.3%. Furthermore, prior research showed that not microcirculation but peripheral temperature, age and APACHE IV predictive mortality scores were related to the Freestyle Navigator sensor accuracy.[9] In addition, an improved next generation Freestyle Navigator II has recently been introduced and showed good utility and sensor performance in critically ill patients.[16]

In the current study and in the study of Flower et al. no interference with clinical care, haemodynamic monitoring or blood sampling was found. This suggests a clinically acceptable level of invasiveness when using an intra-arterial CGM device, especially because critically ill patients are already subjected to invasive treatment and monitoring.

Conclusions

This small observational study has shown that the sensor accuracy of both intra-arterial and subcutaneous sensors was similar in cardiac surgery patients with an MARD of 11-12%. The IA-CGM system directly measured arterial blood glucose and did not interfere with clinical care. The SC-CGM system provided a less invasive alternative with similar performance.

Funding sources
This work was funded by Glumetrics inc. Irvine, CA, USA.

Acknowledgments
We express our gratefulness to the medical, nursing and ICT staff from the OLVG intensive care unit.

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7

Poor Agreement of Computerized Calculators for Mean Amplitude of Glycaemic Excursions

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Diabetes Technology & Therapeutics 2014; 16(2):72-5

Abstract

Background

Glucose variability has been identified as a predictor of hypoglycaemia and has been associated with mortality in critically ill patients without diabetes. A popular metric to quantify glucose variability is the mean amplitude of glycaemic excursions (MAGE). The ‘‘ruler and pencil’’ approach to calculate MAGE is operator-dependent and time-consuming for analysis of continuous glucose monitoring data. Therefore, several computer software programs have been developed for the automated calculation of MAGE. The aim of our study was to evaluate the agreement of currently available MAGE calculators when applied to the same set of continuous glucose monitoring (CGM) traces.

Materials and Methods

Four software programs for calculation of MAGE were identified and used to calculate MAGE of 21 CGM traces from seven patients with type 1 diabetes. Subsequently, the median MAGE per calculator was calculated. The correlation between the MAGE calculators was evaluated by Spearman’s correlation analysis. Between-group comparison was performed using analysis of variance.

Results

The median MAGE (interquartile range) per calculator was 8.7 (7.1–10.7), 6.7 (5.5–8.6), 6.7 (5.2–8.6), and 5.8 (4.3–7.1), which was statistically different overall ($P < 0.001$). The correlation coefficients between the calculators ranged from 0.787 to 0.999.

Conclusions

Available computer programs developed to calculate MAGE show varying agreement. Although software programs for the calculation of MAGE would seem attractive to assess glucose variability, their use has limitations by different outcomes, in the absence of a gold standard.

Introduction

Although there seems to be no clear role for glucose variability in the pathogenesis of micro- and macrovascular complications of diabetes mellitus[1], glucose variability has been identified as a predictor of hypoglycaemia[2–5] and has been convincingly associated with mortality in critically ill patients without diabetes.[6,7] With the increased availability of continuous glucose monitoring (CGM), which rapidly generates a large amount of data, clinicians would benefit from an easy-to-understand metric to quantify glucose variability. Even though numerous measures have been proposed to quantify glucose variability, there is no ''gold standard,'' and many of them are not useful in clinical practice.[1]

The mean amplitude of glycaemic excursions (MAGE), based on the arithmetic mean of differences between consecutive peak and nadirs of differences greater than 1 SD of mean glucose, is designed to assess major, especially postprandial, glucose swings and exclude minor ones.[8] Together with SD, it has become a popular metric to assess glucose variability. However, MAGE has numerous limitations: it is unclear whether excursions smaller than 1 SD should indeed be discarded, it does not take the frequency of excursions into account, and there is a difference in outcome when ascending or descending limbs are used for calculation of MAGE.[9,10] Moreover, the ''ruler and pencil'' approach to estimate MAGE, which is often used by researchers when calculating MAGE, is time-consuming and operator-dependent for analysis of a large number of CGM data.[10–12] Therefore, computerized determination has been recommended.[11]

Several computer software programs have been developed for the calculation of MAGE.[9,12–14] The original MAGE definition, however, does not give sufficient detail to develop a clear computing algorithm.[9,11] Thus, the question arises whether the available computer software programs produce identical MAGE values for a given glucose trial. The aim of the study was to evaluate the agreement of currently available automated MAGE calculators when applied the same set of CGM traces.

Materials and Methods

CGM data collection

CGM traces were obtained from seven patients with type 1 diabetes (mean age, 42 – 12 years) who had previously participated in a clinical study designed for the development of an artificial pancreas. All patients were admitted three times for a duration of 24 h to the clinical research center. At least a 1-week interval was set between the hospital admissions. After clinical research center admission (6:00 p.m.), patients were provided with a subcutaneous CGM sensor (SEVEN® Plus; DexCom, San Diego, CA), and CGM measurements were started after calibration according to the manufacturer's specifications.

Patients received three meals during their stay in the CRC, namely, dinner at 7:00 p.m. (80 g of carbohydrates), breakfast at 8:00 a.m. (50 g of carbohydrates), and lunch at noon (60 g of carbohydrates). At 3:00 p.m. an exercise test was performed. CGM measurements finished at 6:00 p.m. with subsequent removal of the sensor.

MAGE calculators

Four currently available software programs for calculation of MAGE from CGM data were used for the purpose of this study: the Web-based application ''GlyCulator,''[13] the Excel® (Microsoft®, Redmond, WA)-enabled workbook ''EasyGV''[14] (©University of Oxford,Oxford, United Kingdom), the MAGE computer program offered by the Diabetes Service Center, Karlsburg, Germany, described by Fritzsche et al.[12], and the automated algorithm for MAGE calculation described by Baghurst et al[9]. In this article, the calculators will be referred to as Glyculator, EasyGV, Fritzsche, and Baghurst, respectively. All calculators first generate the SD of a given CGM trace. Subsequently, Glyculator and EasyGV both calculate a single MAGE value from a given CGM trace without use of a graphical display of the glucose values. In contrast, the Fritzsche and Baghurst calculators generate a graph of the CGM values, which is then used to calculate MAGE. Both Fritzsche and Baghurst give the user additional options for the calculation of MAGE. Specifically, Fritzsche et al.[12] proposed in their published article that incomplete excursions at the start or end of a glucose profile should not be included in the calculation of MAGE. Therefore, the Fritzsche calculator lets the user choose whether or not to consider the first and/or the final glucose value of the CGM trace as a start or end point of a glucose excursion. This results into four different MAGE values per CGM trace. The Baghurst calculator calculates MAGE of all upward excursions (MAGE+), downward excursions (MAGE-), and an average of all excursions (MAGE.avge).

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Data analysis

Twenty-one CGM traces were reformatted to meet the requirements of the computer programs. SD and MAGE were calculated for each CGM trace with use of the available MAGE calculators. One single SD for each CGM trace was used because CGM traces did not exceed the maximum of 24 h. The SD of each calculator was compared with the SD calculated from the raw CGM data. Missing SD or MAGE values were identified and recorded. For the calculation of MAGE of Fritzsche, we changed the timestamps of the original CGM readings in a way that the CGM trace ''started'' at 0:00 a.m. (instead of 6:00 p.m.) and ended at 11:59 p.m. This was needed because the Fritzsche calculator was only able to calculate MAGE per day and not per CGM trace if a trace extended from before to after midnight. In order to obtain an adequate comparison among the different MAGE calculations, we used one MAGE calculation per CGM trace per calculator. We selected the

MAGE calculation of Fritzsche in which both the first and final glucose values were taken into account. The MAGE of Baghurst (i.e., either using MAGE+ or MAGE-) was selected by exploring the direction of the first excursion of the generated graph of each CGM trace. These selections were based on the original description of MAGE,[8] which graphically shows that the first and final glucose values of a CGM trace are considered as the start or end point of a glucose excursion and that the direction of the first excursion is used to either include the up- or downward excursions in the calculation of MAGE.

Statistical analysis

Data are presented as mean ± SD values or median (interquartile range), as appropriate. The correlation between the MAGE values obtained by the different MAGE calculators was evaluated by Spearman's correlation analysis. A correlation coefficient (r) of at least 0.95 was considered a sufficient correlation, given the fact that the calculators aim at assessing the same metric. Between-group comparison of the median MAGE per calculator was performed using analysis of variance (Friedman's test). Post hoc testing was performed by use of Dunn's multiple comparison test. Finally, Bland–Altman plots were used to assess the agreement of the methods over the range of MAGE values. A P value of < 0.05 was considered significant.

Results

Of the 21 provided CGM traces the mean number of CGM readings was 274 (268–281), mean duration of CGM readings was 23.2 (23.0–23.3) h, mean glucose was 8.4 (7.0–9.2) mmol/L, and mean SD was 3.0 (2.2–3.6) mmol/L.

All calculators were able to calculate a SD from the given CGM traces, and those were similar to the SD generated from the raw CGM data. The Glyculator, Fritzsche, and Baghurst calculators were able to calculate MAGE from all the provided CGM traces, whereas EasyGV showed a missing value in one out of 21 provided CGM traces. The reason for this missing value could not be determined.

Table 1 shows the correlation coefficients for MAGE calculation between the calculators, which ranged from 0.787 to 0.999. The median MAGE and corresponding interquartile ranges per calculator are shown in Figure 1: Glyculator, 8.7 (7.1–10.7); Fritzsche, 6.7 (5.5–8.6); Baghurst, 6.7 (5.2–8.6); and EasyGV 5.8 (4.3–7.1). Between-group comparison showed a significant overall difference between the median MAGE of all four calculators ($P < 0.001$) (Fig. 1). Post hoc analysis showed a significant difference between Glyculator versus Fritzsche, Baghurst, and EasyGV ($P < 0.01$ for all). We finally used Bland–Altman plots to assess the agreement of the MAGE calculators over the range of MAGE values (plots not shown). Mean differences were 2.41 ± 2.56 (Glyculator vs. EasyGV), 1.81 ± 1.22

(Glyculator vs. Fritzsche), 1.84 ± 1.23 (Glyculator vs. Baghurst), -0.60 ± 2.56 (EasyGV vs. Fritzsche), 0.57 ± 2.55 (EasyGV vs. Baghurst), and 0.03 ± 0.11 (Fritzsche vs. Baghurst) mmol/L, respectively. The differences between the calculators were independent of the absolute MAGE values.

Table 1. Spearman's Correlation Analysis Among Mean Amplitude of Glycaemic Excursions Calculators

	Glyculator	Easy GV	Fritzsche
Glyculator	–	–	–
Easy GV	0.787	–	–
Fritzsche	0.909	0.873	–
Baghurst	0.910	0.871	0.999

$P < 0.001$ for all comparisons.

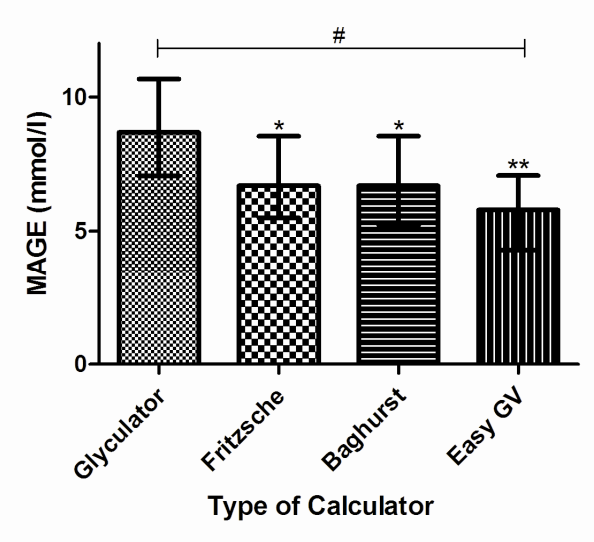

Figure 1. Variation in mean amplitude of glycaemic excursions (MAGE) calculation per type of calculator.
Data are shown as the medians with corresponding interquartile ranges. Statistical significance was determined using the Friedman test followed by Dunn's post hoc test. Between-group comparison showed a significant overall difference among all calculators: # overall $P < 0.001$. *$P < 0.01$, **$P < 0.001$ compared with Glyculator in post hoc analysis.

Discussion

The current study shows varying agreement among the available computer programs developed and validated to calculate MAGE. A good agreement is only found between Fritzsche and Baghurst and not between the other calculators. Furthermore, an overall significant difference among the median MAGE values of all four calculators was found, in which Glyculator was most deviant. To our knowledge, this is the first article comparing different MAGE calculators applied on identical CGM datasets.

In view of these varying correlations among the currently available MAGE calculators, which are intended to measure the same MAGE, certain important issues should be considered. MAGE calculation was initially developed using hourly glucose samples, and it has never been formally validated for calculation from CGM data. Also, there is no ''gold standard'' for the calculation of MAGE. The somewhat complex explanation how MAGE should be determined in the original description for MAGE calculation by Service et al.[8] may have led to various interpretations how to translate this into a computed algorithm. It should be noted that we made some choices in how to apply the Baghurst and Fritzsche calculators, according to what we thought would be most consistent with the original description of MAGE.[8] For the Baghurst calculator, we determined per trace whether the first excursion was an upstroke or downstroke, rather than applying MAGE+, MAGE-, or MAGE.avge. For the Fritzsche calculator, we decided to include both the first and last data point, rather than deleting these. With these choices, a correlation of 100% between these two calculators was seen, arguing for the notion that these are the correct choices and that with these choices these calculators perform a correct calculation of MAGE. Likely as this may be, we still cannot be certain that these are the correct choices.

The exact way MAGE calculation is performed by Glyculator and EasyGV could not be determined from either the original descriptions or the software. Moreover, a graphical display of a glucose trail, such as provided by Fritzsche and Baghurst, seems a requirement for the automated calculation of MAGE. Given the results of this study it becomes even more evident that MAGE is a complex measure to implement in clinical practice. In addition, considering the high correlation between MAGE with the overall SD,[11] one should question whether the use of MAGE offers any advantage over other measures in terms of its ability to determine glucose variability. SD may be superior in terms of its definition, ease, and consistency of computation,[11] although it remains a measure of dispersion rather then glucose variability. Mean absolute glucose change may become the standard for glucose variability.[7,10]

This study should be viewed in light of its strengths and limitations. The main strength of the study was the considerable numbers of CGM traces that were systematically analysed

by the available calculators. A possible concern regarding this study is that we did not compare the results of the MAGE calculators with the graphical ‘‘ruler and pencil’’ approach, which possibly can be seen as the ‘‘gold standard’’ method in calculating MAGE. Although the interoperator variability for the manual calculation of MAGE has not formally been investigated, it seems unlikely that this will be less than for the available automated calculators. Also, given the amount of data, automated calculation seems preferable.

Conclusion

Although validated software programs for the calculation of MAGE would appear useful for clinicians in order to assess glucose variability, one should be aware of the operator dependency or interoperator variability of the available automated MAGE calculators. This limitation adds to the previously reported limitations of MAGE.

Acknowledgments
We acknowledge the AP@home Consortium for giving us access to the continuous glucose monitor trials used for our analysis.

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8

The incidence of diabetes mellitus following pulmonary embolism: a retrospective cohort study

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Journal of Thrombosis and Haemostasis 2012; 10: 2628–30

Introduction

Venous thromboembolism (VTE), including deep vein thrombosis and pulmonary embolism (PE), is often accompanied by acute hyperglycaemia or 'stress-hyperglycaemia'.[1] Conversely, growing evidence suggests that both chronic and acute hyperglycaemia contribute to coagulation activation and hypofibrinolysis, resulting in a prothrombotic state.[2,3]

The clinical consequences of the presence of stress-hyperglycaemia during VTE have been assessed in different patient settings. In an outpatient population, hyperglycaemia at presentation was shown to be associated with VTE, with a clear linear relation between glucose levels and risk of VTE.[4] Furthermore, in orthopedic patients undergoing total hip arthroplasty there was an association between stress-hyperglycaemia and VTE.[5] In addition, a recently published large retrospective cohort study in >13,000 patients with acute PE has shown that elevated admission glucose levels were present in the majority of patients and were independently associated with 30-day mortality.[6]

What could explain the presence of stress-hyperglycaemia during VTE? First, elevated glucose levels during a VTE can result from the physical stress response (inflammatory and counter-regulatory hormone action) induced by the VTE event itself. Second, undiagnosed impaired glucose tolerance may be present in a proportion of patients before the VTE itself and may therefore have contributed to the development of thrombosis. Both may be operative in different subjects, but may also coincide in the same subject. As stress-hyperglycaemia may be considered as a manifestation of impaired glucose tolerance, which in itself frequently evolves into diabetes mellitus (DM), one would expect an increase in incidence rate of DM in patients after a diagnosis of VTE. In this study we tested the hypothesis that the risk of DM in subjects with PE is increased compared with subjects without PE.

Methods

Data collection

Data were derived from the PHARMO Record Linkage System (RLS), which consists of multiple observational databases linked on a patient level, covering over three million individuals in defined areas of the Netherlands. For the purpose of this study, data on drug prescribing from the community pharmacy database and on hospitalization from the Dutch National Medical register were used. Drugs are coded according to the Anatomical Therapeutic Chemical (ATC) classification. The hospital admission and discharge codes are coded according to the International Classification of Diseases, 9th Revision (ICD-9-CM).

All subjects with a first hospitalization for PE (ICD 4151) between 1998 and 2009 were identified (PE-cohort). Exclusion criteria were: known DM defined as prescription of antidiabetic medication (ATC A10A-A10B-A10X); known malignancy defined as hospitalization (ICD 1400-2400) within 5 years prior to the diagnosis of PE; and systemic use of glucocorticosteroids (ATC H02AB-QH02AB) within 6 months before the diagnosis of PE. Subjects without a diagnosis of PE (the non-PE cohort) were derived from the same source population from which the PE patients were identified. Selection was performed randomly, taking into account the male/female ratio, date of birth (±1 year) and geographical region of the PE subjects. Subsequently, the same exclusion criteria were applied in the non-PE cohort as were used in the PE-cohort. The date of hospital discharge for PE was considered to represent the start of follow-up (i.e. index date). Non-PE subjects were assigned the same index date as their matched PE subject. Each subject was followed for 5 years from their index date to the occurrence of the study outcome or censoring (last available prescription or admission in PHARMO RLS or in the Dutch registry for mortality), whichever came first.

Statistical analysis

The main outcome of the study was the onset of DM within 5 years after the index date. DM was defined as the prescription of glucose-lowering therapy, either orally or subcutaneously (ATC A10A-A10B-A10X) as registered in the PHARMO RLS. The association between PE and study outcome was explored by means of the Kaplan–Meier method and formally tested using the log rank test. Subsequently, a Cox proportional-hazards regression model was used to adjust for age. Data management and statistical analyses were performed with SAS software version 6.12 (SAS Institute Inc., Cary, NC, USA) and SPSS software version 18.0 (SPSS Inc., Chicago, IL, USA).

Results

The PE-cohort consisted of 5045 subjects, whereas the non-PE cohort contained 6785 subjects. The mean age ± SD of the studied cohorts at baseline was 58 ± 18 years in the PE cohort and 56 ± 18 years in the control cohort. In both cohorts, sex was distributed similarly (44% male subjects). During 5 years of follow-up, DM occurred in 168 (3.3%) subjects with PE and in 234 (3.4%) subjects without PE (P = 0.717). After 5 years of follow-up, the Kaplan–Meier estimate of DM-free survival (standard error) was similar in both groups; 0.952 (0.004) in the PE cohort and 0.952 (0.003) in the non PE-cohort (P = 0.543), as can be seen in Fig. 1. Using a Cox proportional-hazards regression model adjusting for age, PE was not associated with an increased risk of developing DM(HR 1.01, 95% CI 0.8–1.2; P = 0.93).

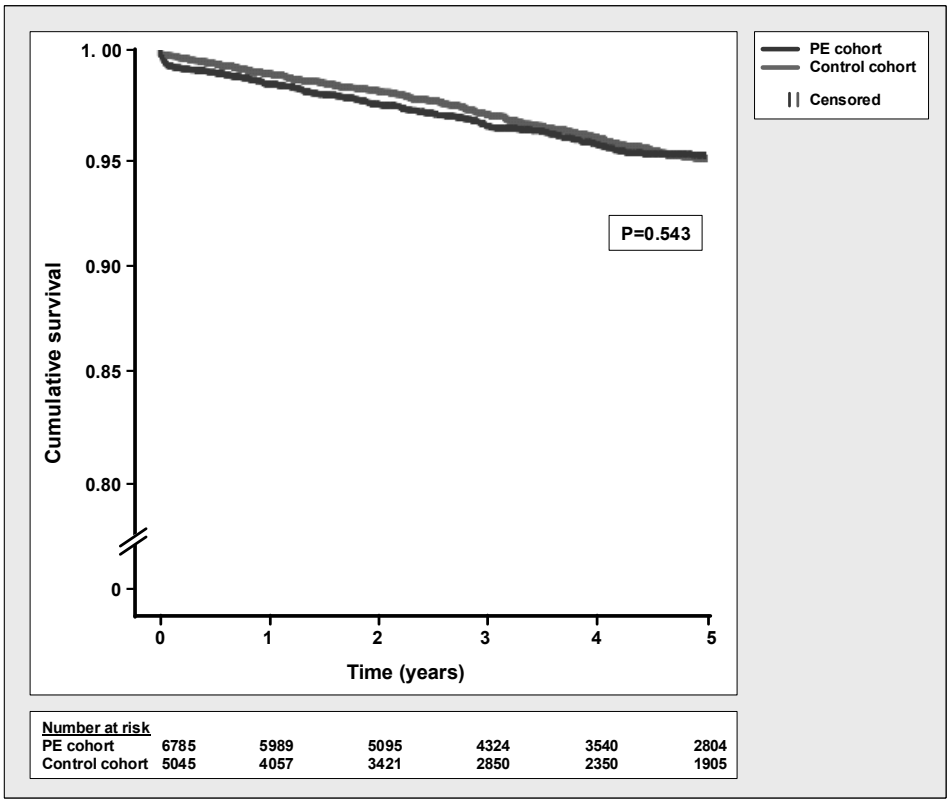

Figure 1. Kaplan-Meier estimates of DM-free survival among patients with and without a diagnosis of pulmonary embolism.

Discussion

In this large population-based registry study, we could not confirm the hypothesis that a diagnosis of PE was associated with an increased risk of DM. We found a similar 5-year incidence of DM of 3% in the studied cohorts. To our knowledge, this is the first study examining the association of a diagnosis of PE and the risk of developing DM. The incidence of DM we found in the non-PE cohort (i.e. control population), 7 per 1000 persons per year, was similar to the estimated mean incidence of DM in the Netherlands based on five general practice records described by Baan et al.[7]

Our findings contribute to ongoing discussions about whether stress hyperglycaemia solely results from the physical stress induced by the venous thrombo-embolic event itself or

whether it may reflect a pre-existent disturbed glucose homeostasis.[4,8] Although disturbed glucose homeostasis will be present in a proportion of patients with PE, the present findings suggest that overall, PE patients do not carry an elevated risk of developing DM. Screening of this population for DM, as is advocated after clinical presentations of atherosclerotic diseases such as myocardial infarction and stroke, does not seem warranted.[9,10]

The main strength of this study was the large cohort of patients with PE, who were followed for a relatively long period. The study design has some obvious limitations, which are inherent to all population-based registry studies. The diagnosis of pulmonary embolism was derived from ICD codes, which could raise concern about accuracy and may contribute to selection bias. However, Casez et al.[11] recently showed that ICD discharge diagnosis codes yield sufficient sensitivity for identifying objectively confirmed PE. Furthermore, subjects diagnosed with DM and treated with diet only are not identifiable as DM subjects in our prescription drug-based database. This may have contributed to an underestimation of the 5-year incidence of DM in both cohorts. Also, information on the pathogenesis of PE is lacking. It might be that in a subgroup of patients with a specific aetiology of PE (i.e. surgery), hyperglycaemia is predominantly explained by physical stress, whereas in patients with unprovoked events a pre-existent disturbed glucose homeostasis may play a more prominent role. Unfortunately, glucose levels and other parameters were not available for this investigation. Finally, because patients were retrieved through hospital admissions, we might have missed patients that may have been treated as outpatients. In the Netherlands, however, guidelines clearly recommend in-hospital treatment of PE.[12]

Conclusion

The results of the present study show a similar 5-year incidence of DM for subjects with and without PE. These findings suggest that PE patients in general are not at increased risk of developing DM, although further investigation in subgroups with a specific pathogenesis of PE would be welcome.

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Lowering blood glucose during hip surgery does not influence coagulation activation

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BBA Clinical June 2015;(3)227–232

Abstract

Background

Hyperglycaemia during and after hip surgery is associated with coagulation activation and an increased risk of venous thromboembolism. Whether lowering of glucose levels during hip surgery diminishes coagulation activation is unknown. We investigated the efficacy of the human GLP-1 analogue liraglutide to lower glucose during and after hip surgery and studied its influence on coagulation activation.

Materials and Methods

A total of 37 obese subjects who underwent hip surgery were randomized to subcutaneous liraglutide or placebo for 4 consecutive days, starting one day prior to surgery. Glucose levels and coagulation indices at three fixed time-points (pre-operative, 2 hours post-operative and 3 days post-operative) were measured.

Results

Liraglutide reduced glucose at day three post-surgery (median glucose (IQR) liraglutide 5.5 (5.2-5.7) vs. placebo 5.8 (5.5-6.2); difference 0.3 mmol/L, $P = 0.04$). Changes in 6 out of 8 coagulation indices studied did not differ between the two groups. Only D-dimer levels were significantly lower in the liraglutide group at day three post-surgery and FVIII levels were significantly higher in the liraglutide group two hours post-surgery.

Conclusion

Although the human GLP-1 analogue liraglutide moderately reduced post-operative blood glucose levels in non-diabetic and prediabetic obese patients undergoing elective hip surgery, no changes were observed with respect to coagulation activation.

Introduction

Patients undergoing hip surgery have a risk to develop postoperative venous thromboembolism (VTE). It is estimated that symptomatic VTE occurs in approximately 0.5 to 2.0% of patients, even if adequate thromboprophylaxis is provided.[1,2] While the procedure-related tissue damage is the major activator of coagulation, several risk factors, such as postoperative immobilization, increasing age and high body mass index, have been associated with a higher incidence of VTE.[3] In addition, we have recently shown that post-surgical 'stress-induced' hyperglycaemia in patients undergoing elective hip surgery is associated with an increased risk for symptomatic VTE, independent of diabetes mellitus and other confounders[4].

That surgery itself can precipitate acute hyperglycaemia, or 'stress hyperglycaemia', is well known and appears to be due to alteration of endogenous hormone production and metabolites.[5] Growing evidence supports the hypothesis that 'stress hyperglycaemia' leads to a hypercoagulable and hypofibrinolytic state.[6] In experimental settings as well as in patients with diabetes, hyperglycaemia contributes to coagulation activation and downregulation of fibrinolytic activity, as demonstrated by increased levels of several procoagulant factors, such as thrombin-antithrombin (TAT) complexes, soluble tissue factor, fibrinogen, von Willebrand (vWF), factor VII, factor VIII and decreased levels of antifibrinolytic factors (plasminogen activator inhibitor-1 (PAI-1)).[7-9] Moreover, hip surgery in patients without diabetes mellitus has been shown to induce hyperglycaemia peaking the days after the procedure, which was followed by a rise of factor VIII, vWF and prothrombin fragment 1+2 (F1+2).[10]

In diabetic patients, the effect of hyperglycaemia on coagulation seems to be modifiable, as improvement of glycaemic control among these patients led to downregulation of coagulation activation.[11,12] Whether establishing glycaemic control during hip surgery will influence the coagulation activation is unknown.

Insulin therapy is the most widely used method to induce glycaemic control. However, insulin therapy is time consuming and is accompanied by an increased risk of hypoglycaemia, which is related to serious morbidity.[13] The human glucagon-like peptide-1 (GLP-1) analogue liraglutide is an alternative glucose lowering agent which acts in a glucose-dependent manner, i.e. it stimulates insulin secretion only when blood glucose levels are above normal. Consequently, it has negligible risk of hypoglycaemia.[14] In the current study we aimed to investigate the efficacy of the human GLP-1 analogue liraglutide to lower glucose during and after hip surgery and its influence on coagulation activation.

Materials and methods

Study design and participants

This was a randomized, double-blind, placebo-controlled trial performed at the orthopaedic department of a teaching hospital (Onze Lieve Vrouwe Gasthuis, Amsterdam, The Netherlands) involving 37 patients. Participants were recruited between August 2012 and September 2013. Inclusion criteria were: men and women between 18 and 75 years of age, scheduled for elective hip surgery, dabigatran used as anticoagulant drug after surgery and signed informed consent. Exclusion criteria were: type 1 or type 2 diabetes mellitus, use of oral corticosteroids, use of Vitamin K antagonists, known coagulation disorders, known active cancer, a history of chronic pancreatitis or idiopathic acute pancreatitis, impaired liver function (defined as alanine aminotransferase (ALAT) 2.5 times upper normal limit) or renal function (defined as serum-creatinine 133 μmol/L for males and 115 μmol/L for females), females of child bearing potential who are pregnant or breast-feeding and spinal anaesthesia. The study protocol was approved by the institutional review board (medical ethical committee of the Academic Medical Center, Amsterdam and Onze Lieve Vrouwe Gasthuis, Amsterdam). All participants provided written informed consent. This trial is registered at the Dutch trial register, www.trialregister.nl, number NTR3547.

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Study procedures

Participants were randomised to receive either liraglutide or matching placebo by block randomisation (block size was 4) via a pre-generated fixed list with successive numbered treatment options. Both participants and investigators were blinded to treatment assignment. Treatment with liraglutide (0.6 mg) or placebo started one day prior to surgery. Participants underwent dose escalation to 1.2 mg/day at the day of surgery until day 3 post-operative. Liraglutide (6.0 mg/ml) and placebo were provided in identical FlexPen® devices (Novo Nordisk A/S, Bagsværd, Denmark) and were given by subcutaneous injection in the abdomen at 5 pm daily. Adverse events were recorded daily by study personnel. The total planned treatment period was 4 days. All participants received general anaesthesia and identical anti-emetic prophylaxis (droperidol 0.625 mg during induction, granisetron 1 mg post-operatively). None of the subjects received corticosteroids. Venous blood samples for laboratory tests were taken at 3 fixed points in time (before induction of anaesthesia, 2 hours after the end of surgery and three days post-operative. All blood samples were taken by venapuncture in the fasting state. In all participants, 220 mg dabigatran once-daily in the morning starting from the day after surgery was given as thromboprophylaxis. All subjects were allowed to resume their daily diet when they were transferred to the surgical ward.

Outcome measures

The primary outcome was the difference in glucose at day 3 post-surgery between the study groups. Secondary outcomes were the difference in coagulation indices at day 3 post-surgery and included prothrombin fragment 1+2 (F1+2), thrombin-antithrombin complex (TAT), plasmin-alpha2-antiplasmin complex (PAP), D-dimer, coagulation factor VIII (FVIII), von Willebrand factor (vWF), antithrombin (AT) and plasminogen activator inhibitor-1 (PAI-1).

Laboratory assessments

All blood samples were centrifuged within one hour at 1500 g at 4ºC for 10 minutes, plasma was separated (separated plasma of citrate samples was centrifuged again for 10 minutes) and stored immediately at -70ºC. Plasma glucose concentrations were measured with a glucose hexokinase method (Roche/Hitachi, Indianapolis, USA). D-dimer, factor VIII activity and AT were measured on an automated coagulation analyser (Siemens BCS-XP system) using protocols and reagents from the manufacturer (Siemens Healthcare Diagnostics, Marburg, Germany). Antigen levels of vWF were assayed by ELISA using antigens from DAKO (Heverlee, Belgium). F1+2 and TAT were determined by ELISA from Siemens Healthcare Diagnostics, PAI-1 was determined by ELISA from BioMed and PAP was determined by ELISA from DRG diagnostica (Marburg, Germany).

Statistical analysis

The study was powered to detect a difference (± SD) of 1.0 ± 0.8 mmol/L in glucose three days post-surgery between the two study groups. This difference was based on a 2 mmol/L increase in glucose level in a prior study[10] and an expected 50% reduction in glucose with use of liraglutide. Taking into account a drop-out rate of 10 percent, the sample size calculation indicated that 18 patients per group were needed in order to detect the effect on glucose between the two study groups with 80% power and an alpha level of 0.05. Analyses were based on the intention-to-treat principle. Data of the patients who were withdrawn from the study before day three post-surgery were used for the analyses as far as possible. Results are expressed as percentages for categorical variables, mean and standard deviation (SD) for continuous normally distributed variables, and median and interquartile range (IQR) for continuous non-normally distributed variables. Groups were compared by using Fisher's Exact test, Student's t test or Mann Whitney rank-sum test where appropriate. Primary and secondary outcomes were analysed by use of the Mann Whitney rank-sum test. In addition, mixed between-within ANOVA analyses were performed to assess the treatment effect over time. A secondary analysis was performed to assess the influence of surgery-induced stress on coagulation. Data from the placebo group were used to assess equality of the laboratory parameters at three time points using the Friedman test. Where the Friedman test resulted in statistical significance, subsequent tests were performed using

the Wilcoxon Signed rank test. All analyses were performed using PASW statistics software version 20.0 (SPSS Inc, Chicago, IL, USA), a P-value of < 0.05 was considered statistically significant.

Results

In total, 37 patients were randomised and 36 received study medication in the trial. Thirty-two patients completed the trial (figure 1). One patient withdrew informed consent prior to start of treatment and was replaced. Two patients in the liraglutide group withdrew from the study due to adverse events (moderate/severe nausea, starting at the dose of 1.2 mg/day). Furthermore, in each study-group one patient discontinued the study due to non-compliance with the protocol (not willing to undergo blood sampling). Baseline characteristics are summarized in Table 1. More women were randomized to the placebo group, which did not reach statistical significance. Most patients included in the trial were overweight (average BMI of 28 kg/m^2).

Table 1. Baseline characteristics of the patients included in the trial.

	Liraglutide (*n* = 19)	**Placebo** (*n* = 17)
Age – years (mean ± SD)	57 ± 12	59 ± 11
Sex, female n (%)	9 (47)	13 (77)
Body-mass index – kg/m² (mean ± SD)	28 ± 5	27 ± 5
Ethnic origin, n (%)		
- White	16 (84)	17 (100)
- Surinam/Antilian	2 (11)	-
- Other	1 (5)	-
Reason surgery, n (%)		
Coxarthrosis	18 (95)	16 (94)
Other	1 (5)	1 (6)
Type of hip implant fixation, n (%)		
Cemented	12 (63)	10 (59)
Cementless	3 (16)	3 (18)
Hybrid[1]	4 (21)	4 (23)
Relevant medical history, n (%)		
Cardiovascular disease	-	-
COPD/Asthma	2 (11)	1 (6)
History of VTE	-	-
HbA1c – mmol/mol (mean ± SD)	38 ± 3	36 ± 3
Duration of surgery in minutes (mean ± SD)	89 ± 23	101 ± 27

COPD: Chronic Obstructive Pulmonary Disease; VTE: venous thrombo-embolism;
HbA1c: glycated haemoglobin. [1]Cup inserted without cement, stem inserted with cement.

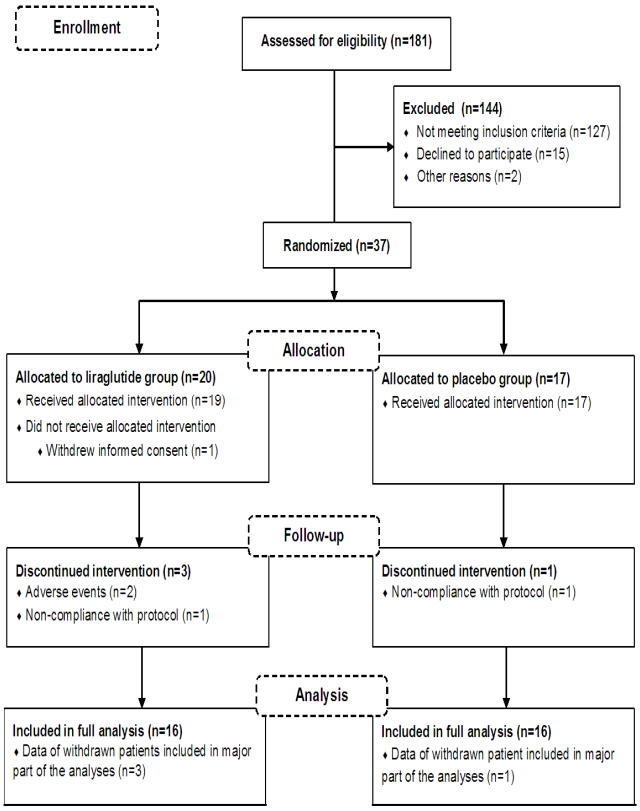

Figure 1. Flow chart of study participants; assessment, randomization and analysis.

Glucose levels

Plasma glucose levels per time point per treatment group are depicted in figure 2. Glucose at day three post-surgery was significantly lower in the liraglutide group (median glucose (IQR) liraglutide 5.5 (5.2-5.7) vs. placebo 5.8 (5.5-6.2); difference 0.3 mmol/L, P = 0.04). However, liraglutide treatment did not significantly reduce glucose levels during the full treatment period (P = 0.36).

Coagulation markers

Figure 3 shows coagulation indices per time point per treatment group. A significant difference between the groups was only found in D-dimer levels at day three post-surgery (median D-dimer (IQR) liraglutide 1.5 (1.2-1.9) vs. placebo 1.9 (1.6-2.4); difference -0.4 mmol/L, P = 0.04) and in FVIII levels two hours post-surgery (median FVIII (IQR) liraglutide 219 (163-243) vs. placebo 132 (118-215); P=0.04). However, liraglutide treatment did not significantly change D-dimer levels (P = 0.56) and FVIII levels (P = 0.28) during the full treatment period.

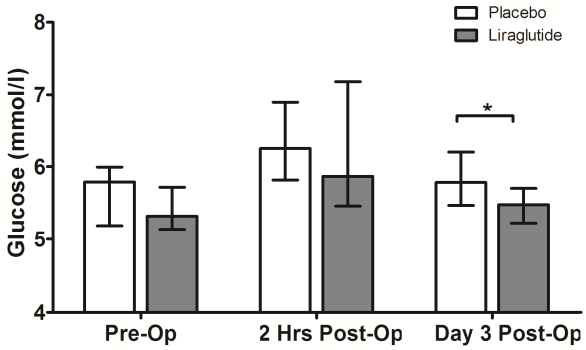

Figure 2. Median peri-operative glucose levels with interquartile range per treatment group. *$P < 0.05$.

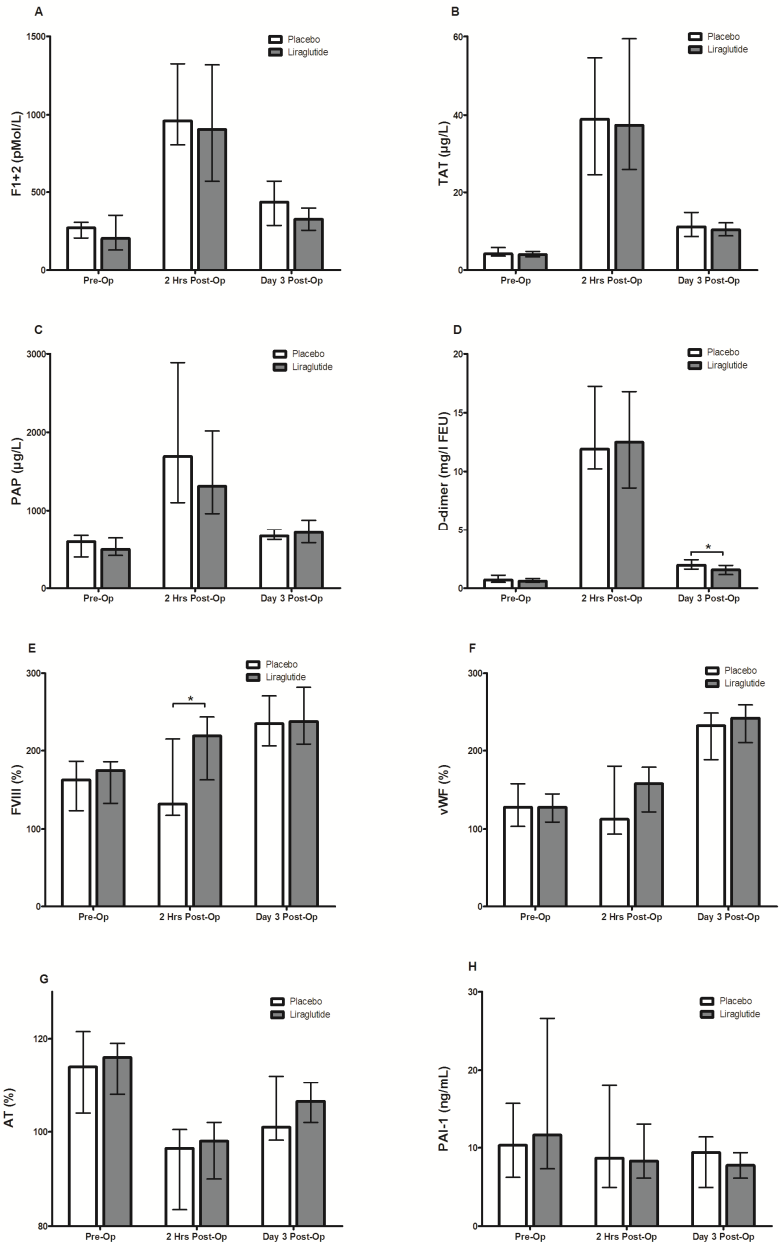

Figure 3. Coagulation markers per treatment group during the study period.
F1+2: prothrombin fragment 1+2; TAT: thrombin-antithrombin complex. PAP: plasmin alpha2-antiplasmin complex; vWF: von Willebrand Factor; AT: antithrombin; PAI-1: Plasminogen Activator Inhibitor-1.

Adverse events

The reported adverse events during the trial are shown in table 2. Common adverse events in the liraglutide group were nausea (47%) and loss of appetite (21%). In the placebo group nausea occurred in 29% of patients. No statistical differences were found between the groups.

Influence of surgery-induced stress on glucose levels and coagulation indices

In the placebo group, glucose levels 2 hours post-operatively significantly increased compared to pre-operative glucose levels (table 3). With regard to coagulation, F1+2, TAT, PAP and D-dimer significantly increased and AT significantly decreased during the post-operative period. FVIII and vWF were significantly increased at day three post-operatively, but not two hours post-operatively (table 3).

Table 2 Adverse events reported during the treatment period.

	Liraglutide (n = 19)	Placebo (n = 17)	*P* -value
Nausea	9 (47%)	5 (29%)	0.32
Vomiting	3 (16%)	-	0.23
Loss of Appetite	4 (21%)	1 (6%)	0.34
Dizziness	3 (16%)	1 (6%)	0.61
Headache	2 (11%)	1 (6%)	1.0
Reaction Injection Location	-	1 (6%)	0.47
Vasovagal Collapse	1 (5%)	-	1.0
Diarrhea	-	-	-
No adverse events reported	7 (37%)	10 (59%)	0.32

Table 3 Peri-operative glucose and coagulation indices at all time-points (placebo group).

	Pre-operative (n=17)	2 hrs post-operative (n=16)	Day 3 post-operative (n=16)	*P* Value
Glucose (mmol/L)	5.8 (5.2-6.0)	6.3 (5.8-6.9)†	5.8 (5.5-6.2)	0.003
F1+2 (pMol/L)	271 (207-308)	963 (810-1326)‡	436 (287-572)‡	< 0.001
TAT (µg/L)	4.2 (3.6-5.8)	38.9 (24.5-54.6)‡	11.1 (8.6-14.8)*	< 0.001
PAP (µg/L)	595 (401-675)	1692 (1104-2889)†	667 (623-753)*	< 0.001
D-dimer (mg/l FEU)	0.7 (0.5-1.1)	11.9 (10.2-17.3)‡	2.0 (1.6-2.4)†	< 0.001
FVIII (%)	163 (124-187)	132 (118-215)	235 (207-271)†	0.001
vWF (%)	128 (104-158)	113 (94-181)	232 (189-250)‡	< 0.001
AT (%)	114 (104-122)	97 (84-101)‡	101 (98-112)†	< 0.001
PAI-1 (ng/mL)	10.3 (6.2-15.7)	8.7 (4.9-18.0)	9.4 (4.9-11.4)	0.41

All data are median with interquartile range. * P < 0.05. All data is presented as median (25th - 75th percentile). The statistical change across the three time periods per laboratory assessment was determined by the Friedman Test. *$P < 0.05$, †$P < 0.01$, ‡ $P < 0.001$ compared to pre-operative levels, in post-hoc analysis. F1+2: prothrombin fragment 1+2; TAT: thrombin-antithrombin complex; PAP: plasmin alpha2-antiplasmin complex; vWF: von Willebrand factor; AT: antithrombin; PAI-1: Plasminogen Activator Inhibitor-1.

Discussion

The present study shows that the human GLP-1 analogue liraglutide moderately reduced post-operative blood glucose levels with 0.3 mmol/L in nondiabetic and prediabetic patients undergoing elective hip surgery. However, this decrease in glucose levels did not influence coagulation activation.

Little is known about the impact of hospital-related hyperglycaemia in non-diabetic orthopaedic patients. Richards *et al.* performed a prospective observational study in stable non-diabetic patients with orthopaedic injuries and showed that stress hyperglycaemia was associated with surgical site infection.[15] However, randomized trials evaluating hyperglycaemia treatment in hospitalized non-diabetic, non-critically ill patients are lacking. This investigation is the first randomized trial that focused on the treatment of

postsurgical stress-induced hyperglycaemia in an orthopaedic non-diabetic population. Interestingly, despite the presence of obesity and prediabetes, in both treatment groups only 25% (n=4 in each group) of the patients exceeded the threshold of stress-induced hyperglycaemia postoperatively as defined by Dungan *et al.* (fasting glucose > 6.9 mmol/L).[5] In addition, none of the patients were hyperglycaemic three days post-surgery. These findings are different from our previous observational study, in which we found increased (non-fasting) mean glucose levels (>7.8 mmol/L) postoperatively from the second postoperative day up to the 4th day after surgery.[10] In order to explain these conflicting results we compared baseline- and treatment characteristics between the studies. Patients included in the previous study were on average 4 years older, the mean duration of surgery was longer (121 vs 101 minutes), their BMI was one point higher and half of the patients received dexamethasone as anti-emeticum, which causes hyperglycaemia post-operatively.[16] Whether these differences do explain the lower rate is unclear.

Overall, our current study population consisted of overweight individuals, with an average BMI of 28 kg/m^2. It is known that obesity is common among patients undergoing hip replacement surgery. Moreover, obesity is a clear risk factor for developing osteoarthritis, the most common indication for hip replacement surgery.[17]

9 Interestingly, 14 of 36 patients (39%) had prediabetes glycated haemoglobin levels (between 38-46 mmol/mol), thus being 'prediabetic'. Twenty-one patients (58%) had glycated haemoglobin levels below 38 mmol/mol and one patient had a glycated haemoglobin level of 47 mmol/mol. With regard to pre-operative fasting glucose levels, 17 of 36 patients (47%) had blood glucose levels between 5.6 and 6.9 mmol/L, thus impaired fasting glucose. It should be mentioned that all patients already received the study-therapy, either verum or placebo, no off-treatment baseline values were available. Only 5 of the 17 patients (29%) who had impaired fasting glucose levels also had HbA1C-levels in the prediabetic range. Perhaps, blood glucose-levels at the day of surgery are already increased due to stress related to the upcoming procedure.

The fact that we did not find a marked increase in glucose levels in the placebo group during the treatment period may have contributed to the small difference in glucose levels (0.3 mmol/L) between the treatment groups three days post-operatively. The smaller difference in glucose levels found in this study may also explain that no clear difference in coagulation indices was observed. Thus, a clear causal relationship between glucose and coagulation activation could not be confirmed with the present study. Results should therefore be interpreted with caution. The statistical difference found in D-dimer- and FVIII-levels may have been multiple testing results and one can argue whether these changes are biologically relevant.

That the surgical procedure activates coagulation is clearly demonstrated by the increase of D-dimer, F1+2 and TAT and the decrease in AT post-operatively. Our findings are in line with previous studies which assessed coagulation activation in orthopaedic surgery.[10,18] Other causes, such as bleeding or vascular damage induced by surgery are more likely to have influenced these coagulation parameters than the relatively modest increase in glucose.

Our study has several limitations. First, one may debate the dose escalation and treatment duration used in this study. In diabetes patients treated with GLP-1, dose escalation from the starting dose (0.6 mg/day) to 1.2 mg/day is applied at least after one week of GLP-1 treatment, partly in order to reduce the risk of gastrointestinal side effects. In addition, steady-state pharmacokinetics for liraglutide is reached after three days of treatment.[19] Since no clinical trial data for liraglutide used for a perioperative blood glucose lowering strategy were available, we considered that the proof-of-principle dosing regimen designed for the current study was a good compromise between titrating too fast, which was likely to result in many side effects, and underdosing, which was likely to give suboptimal glucose lowering. Starting liraglutide earlier before surgery did not seem attractive, as these patients would not be hyperglycaemic before surgery.

Second, the placebo group consisted of a non-significantly larger number of female subjects compared to the liraglutide group, despite of the randomisation procedure. In order to assess any effect modification by sex, analyses were also performed for each gender separately. There could perhaps be a minimally larger effect in glucose lowering in females (difference in median glucose 0.4 mmol/L, $P = 0.02$) than in males (difference in median glucose 0.3 mmol/L, $P = 0.26$). It should be noted that comparisons for each gender separately were based on a very small sample size. So this difference should be interpreted cautiously, since it could be the result of random error or confounding.

Third, all laboratory assessments were performed when patients were already on treatment. Therefore, we were not able to include baseline values without treatment as covariate in our analyses. As all subjects who were participating in this trial were non-diabetic, glucose values were expected to be in normal range and taking a fasting baseline sample before hospital admission was not feasible.

Finally, the use of dabigatran as thromboprophylaxis may have influenced the levels of several coagulation markers when patients did receive thromboprophylaxis.[20] However, all subjects in our trial received identical anticoagulant therapy, so dabigatran would have affected both groups similarly.

Conclusion

The use of the human GLP-1 analogue liraglutide in non-diabetic and prediabetic patients undergoing elective hip surgery moderately reduced post-operative blood glucose levels but did not change coagulation activation.

Acknowledgements
This was an investigator-initiated trial, supported financially by Novo Nordisk Inc. The funding source had an advising role in trial design details, but had no role in the conduct of the analyses, interpretation of the data or in the decision to approve publication. We further acknowledge the Department of Orthopaedics and Anesthesiology from the Onze Lieve Vrouwe Gasthuis for their cooperation; the technicians from the Department of Experimental Vascular Medicine at the Academic Medical Center, Amsterdam, and Elly Schipper-Kuipers from the Laboratory of Clinical Chemistry at the Onze Lieve Vrouwe Gasthuis, Amsterdam for the excellent laboratory support. Lastly, we would like to acknowledge prof. dr. Harry Büller for his advice and consultation.

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10

Summary and final considerations

M.K. Sechterberger

The presence of three domains of dysglycaemia—hyperglycaemia, hypoglycaemia and increased glucose variability—in acute illness has received quite some attention in the medical literature, especially with regard to their relationship to patient outcomes in different patient populations. However, controlling blood glucose levels in hospitalized patients has yielded both favourable and detrimental effects. Glycaemic control appears to be a complex interplay of various elements, or, metaphorically, 'a bittersweet symphony'. This thesis focuses on epidemiology, monitoring and treatment of in-hospital dysglycaemia in order to optimize in-hospital glycaemic control.

Chapter 2 gives an overview of the major studies performed in the last two decades to investigate the effect of glycaemic control in hospitalized patients. Glycaemic control in three different patient populations (the critically ill, those admitted to the coronary care unit and those admitted to general wards) is highlighted. Overall, the contradictory outcomes from the clinical trials performed so far cannot provide us with a clear answer on how to best control in-hospital dysglycaemia. Moreover, it emphasizes that in-hospital glycaemic control is a highly complex problem. Whereas for several years 'tight' glycaemic control with insulin therapy was the standard therapy to treat hyperglycaemia in critically ill patients, as was recommended by worldwide clinical guidelines, the current consensus is to maintain a moderate glucose target (7.8-10.0 mmol/L), thereby correcting hyperglycaemia, while avoiding hypoglycaemia and high glucose variability. Further clinical research toward in-hospital glycaemic control in hospitalized patients is warranted.

Chapter 3 establishes the impact of a diagnosis of diabetes on the relationship between glycaemic control and mortality in critically ill patients. In a large observational study which included over 10,000 critically ill patients, four different measures of glycaemic control—mean glucose, glucose variability, hypoglycaemia (<2.2 mmol/L), and low glucose (2.3 to 4.7 mmol/L)—were related to intensive care unit (ICU) mortality. The presence of diabetes affects the association between three out of four measures of glycaemic control and ICU mortality. Specifically, a U-shaped relationship between mean glucose and ICU mortality is found in the non-diabetes population, whereas no clear association is found in the diabetes population. High glucose variability is only related to ICU mortality in the non-diabetes cohort. The occurrence of hypoglycaemia (≤ 2.2 mmol/L) is related to ICU mortality in both populations and should be avoided. Additionally, the cut-off value for detrimental low glucose in the non-diabetes population (4.9 mmol/L) is higher than in the diabetes population (3.5 to 3.9 mmol/L). Interestingly, the results of our study are remarkably consistent with another large observational study of Krinsley and colleagues. Taken together, the studies have clinical implications for clinical practice. Patients with diabetes may tolerate a wider glucose range and avoidance of

hypoglycaemia seems even more important than in non-diabetic patients. Likely, successful management of all three domains of glycaemic control will require the use of continuous or nearly continuous technologies. To date, such technologies are being tested, but are not ready yet for widespread clinical use in a critical care setting.

In **Chapter 4,** a comparison is made between type 1 and type 2 diabetes patients admitted to the ICU with regard to patient- and admission-related characteristics and glycaemic control. Contrary to expectations, a low proportion of type 1 diabetes patients admitted to the ICU is found: only 2% (n=27) of diabetes patients are classified as type 1 diabetes, the remaining (98%, n=1547) are type 2 diabetes patients. Type 1 diabetes patients are younger, have a lower BMI and are more frequently admitted to the ICU for medical admissions. Overall glycaemic control is not different, apart from glucose variability being 20% higher in the type 1 diabetes group. The small sample size of type 1 diabetes patients hampered us to analyze any differences in the association between glycaemic measures and ICU mortality in the two diabetes cohorts. Whether type of diabetes impacts the association between glycaemic measures and ICU mortality needs to be investigated in a larger group of type 1 and type 2 diabetes patients.

Chapter 5 focuses on the use of a subcutaneous continuous glucose monitoring (CGM) device to guide insulin treatment in critically ill patients. A randomized controlled trial which included 177 subjects was performed to study the safety and efficacy of CGM-driven glucose regulation compared to point-of-care measurement driven glucose regulation. In addition, nursing workload and daily costs were assessed. All patients received subcutaneous CGM. CGM data were blinded in the control group, whereas in the intervention group these data were used to feed a computerized glucose regulation algorithm. The same algorithm was used in the control group, fed by intermittent point-of-care glucose measurements. The results show that subcutaneous CGM to guide insulin treatment in critically ill patients is as safe and effective (similar incidence of hypoglycaemia and similar percentage of time in target range) compared to intermittent point-of-care measurements. Furthermore, a significant reduction in daily nursing workload for glucose control and daily costs was found when using the subcutaneous CGM device for glucose regulation. A new algorithm designed for frequent measurements may further improve the results and is a necessary step towards closed-loop glucose control at the ICU.

Chapter 6 presents accuracy results of a newly developed intra-arterial CGM device, as compared to a subcutaneous CGM device in post-cardiac surgery patients admitted to the ICU. The devices differ both in positioning and in technology used for glucose measuring. The results show similar accuracy for both the intra-arterial and the (less invasive) subcutaneous CGM device. The suboptimal performance of the intra-arterial CGM device is mainly attributed to signal loss during routine patient care activities, sub-optimal

securement and possible interference with medication. Further improvements in sensor technology and accuracy, so that CGM devices can be used safely and conveniently in a critical care setting, are required.

With the increased availability of CGM, clinicians would benefit from an easy-to-understand metric to quantify glucose variability. A widely used though also criticized metric is the mean amplitude of glycaemic excursions (MAGE). One of the reasons it has been criticized is a 'ruler and pencil' method often used to assess MAGE, resulting in operator dependency. Therefore computerized assessment was proposed, and several software tools are available. **Chapter 7** provides us insight in the agreement of computerized programs to calculate the MAGE. It turns out that the available computer programs developed and validated to calculate MAGE show varying agreement. Although software programs for the calculation of MAGE would seem attractive to assess glucose variability, their use is thus limited by different outcomes and in the absence of a gold standard.

The last two chapters focus on the consequences of stress-induced hyperglycaemia on coagulation activation. Growing evidence support the hypothesis that both chronic and acute hyperglycaemia contribute to a prothrombotic state (coagulation activation and hypofibrinolysis), which predisposes patients to arterial and venous thromboembolic events. What has not been elucidated yet is what exactly explains the presence of hyperglycaemia during a thromboembolic event. It could be either that elevated blood glucose levels during a thromboembolic event result from the physical stress response induced by the thrombotic event itself, or that it reflects a pre-existent disturbed glucose homeostasis. If the latter, and stress-induced hyperglycaemia is considered to be in part a manifestation of impaired glucose tolerance, which in itself frequently evolves into diabetes, one would expect an increase in incidence rate of diabetes in patients after a diagnosis of a thromboembolic event. **Chapter 8** describes the results of a population-based registry study performed to test the hypothesis that the risk of diabetes in subjects with pulmonary embolism (PE) is increased compared with subjects without pulmonary embolism. It shows a similar 5-year incidence of diabetes for subjects with and without PE. These findings suggest that PE patients in general are not at increased risk of developing diabetes. Screening of this population for diabetes does not seem warranted, although further investigation in subgroups with a specific pathogenesis of PE (i.e. immobilization, surgery and trauma, malignancy, acute critical illness) is needed.

Although the amount of observational data which describes the relationship between stress-induced hyperglycaemia and coagulation activation is substantial, randomized trials evaluating the effect of glucose lowering therapy on coagulation activation in hospitalized, non-diabetic, non-critically ill patients are lacking. **Chapter 9** presents the results of a

randomized controlled trial performed to examine the effect of the human GLP-1 analogue liraglutide, a once-daily subcutaneous glucose lowering agent, in patients undergoing hip surgery with stress-induced hyperglycaemia and its influence on coagulation activation. Patients were allocated to receive either liraglutide or placebo treatment starting one day prior to surgery until day three post-operatively. The results show a significant albeit moderate reduction in glucose level (0.3 mmol/L) in patients treated with liraglutide. However, this decrease in glucose level did not convincingly influence coagulation activation. Thus, a causal relation between glucose lowering and altered coagulation activation in a non-diabetic orthopaedic patient population could not be confirmed. This result is important in view of all the epidemiological evidence supporting a relationship between hyperglycaemia and thrombosis.

Final considerations

Taken together, this thesis provides some insights with regard to in-hospital glycaemic control both in the ICU-setting and non-ICU setting. Despite these insights, the symphony is still 'bittersweet and not fully 'sweetened'. New research topics have arisen and should be addressed in future research.

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First and foremost, an improved understanding of the pathogenesis of dysglycaemia in hospitalised patients, whether they have a prior diagnosis of diabetes or not, may well lead to better targeted therapies. Future studies are likely to benefit from more precise classification of patients according to their pre-existing glycaemic control and severity of acute glycaemic disturbances.

Furthermore, glucose monitoring technology should be advanced in the near future to the likely benefit of critically ill patients. Reliable and accurate measurement devices are essential and CGM devices need to be validated uniformly in terms of accuracy and reliability. Most important, however, will be the impact of device use on clinical outcomes, including improved glycaemic control, fewer hypoglycemic episodes and glucose variability. This is of far more relevance to patients and clinicians than small differences in accuracy.

In view of better sensor technology likely to become available in the near future, the development of closed-loop glucose control systems seems the way forward. The most promising results are to be expected from a randomized controlled trial, which will investigate the feasibility and efficacy of an automated closed-loop glucose control system based on subcutaneous continuous glucose measurements in critically ill adults. When writing this thesis, a study protocol is being reviewed by the ethical committee and

important technical preparations to set up communication between the different elements (subcutaneous sensor, algorithm, remote pump control) are in progress.

Novel therapeutic strategies that treat hyperglycaemia and reduce glycaemic variability, but are associated with minimal risk of hypoglycaemia, merit evaluation. Incretin-based therapy in the critically ill as well as in a peri-operative setting remains appealing. Both insulinotropic and glucagonostatic effects of GLP-1 are likely to be effective in the complex pathogenesis of stress-induced hyperglycaemia.

Another novel therapeutic strategy is the concept of 'therapeutic nutrition' instead of 'supportive nutrition' in critical care. In this regard, Glucerna®, a reduced-carbohydrate, modified-fat, fiber-containing enteral formula, is designed to improve glycaemic control in patients prone to hyperglycaemia. The potential role for Glucerna as a non-insulin alternative to better control glucose levels in critically ill patients will be investigated in the near future.

Lastly, future research with regard to the consequences of stress-induced hyperglycaemia on coagulation should first assess which particular in-hospital patient populations are at risk for thromboembolic events and would benefit from glycaemic control. Furthermore, the effect of glucose lowering therapy on coagulation should be reproduced and further studied in a randomized controlled setting to definitively prove or reject causality of the often described association between hyperglycaemia and coagulation activation.

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Nederlandse samenvatting

M.K. Sechterberger

Aan het eind van de negentiende eeuw beschreef de vooraanstaande Franse fysioloog Claude Bernard in zijn boek "*Leçons sur le diabète et la glycogenèse animale"* een opvallend experiment: met een naald puncteerde hij de vierde hersenventrikel van een konijn wat leidde tot een imposante tijdelijke verhoging van de bloedsuiker (hyperglycemie) en glucose-uitscheiding in de urine. Met deze 'piqûre diabetique' beschreef Bernard het vóórkomen van hyperglycemie tijdens acute schade ('punctie'). Tegenwoordig spreken we van acute hyperglycemie of 'stressgeïnduceerde hyperglycemie' als sprake is van hyperglycemie tijdens een pathogene stressor, zoals een operatie of ernstige ziekte. Ook te lage bloedsuikers (hypoglycemieën) en een sterke schommeling in bloedsuikers (glucose variabiliteit) komen voor. Samen vormen zij de drie domeinen van 'dysglycemie'. Glucoseregulatie bij ziekenhuispatiënten blijkt een complex samenspel van factoren te zijn waarin zeker ruimte is voor optimalisatie. In het eerste deel van dit proefschrift richten we ons in het bijzonder op glucoseregulatie van ernstig zieke patiënten die opgenomen zijn op de intensive care. De laatste hoofdstukken richten zich op de gevolgen van stressgeïnduceerde hyperglycemie in relatie tot het stollingssysteem bij patiënten met een longembolie en bij patiënten die een heupoperatie ondergaan.

Hoofdstuk 2 geeft een overzicht van de huidige literatuur met betrekking tot het effect van glucoseregulatie in drie verschillende populaties van ziekenhuispatiënten (patiënten die verblijven op een intensive care, op de hartbewaking of op chirurgische of niet-chirurgische afdelingen). De tegenstrijdige resultaten van de verscheidene studies onderstrepen de hoge complexiteit die glucoseregulatie bij ziekenhuispatiënten met zich meebrengt. De huidige consensus is dat middelhoge streefwaarden voor glucose moeten worden nageleefd om daarmee zowel hyperglycemie, hypoglycemie als hoge glucose variabiliteit te vermijden.

Hoofdstuk 3 beschrijft de invloed van de diagnose diabetes in relatie tot dysglycemie en de kans op overlijden bij ernstig zieke patiënten die opgenomen zijn op de intensive care. In twee verschillende cohorten (intensive care patiënten met en zonder diabetes) werden vier verschillende domeinen van glucoseregulatie onderzocht, namelijk het gemiddelde glucose, glucose variabiliteit, het voorkomen van ernstige hypoglycemie (< 2.2 mmol/L) en het voorkomen van milde hypoglycemie (2.3-4.7 mmol/L). Het gemiddelde glucose en de glucosevariabiliteit bleek alleen bij de patiënten zonder diabetes gerelateerd te zijn aan overlijden. Ernstige hypoglycemie (<2.2 mmol/L) was in beide cohorten gerelateerd aan overlijden. Daarnaast kwam naar voren dat milde hypoglycemie bij patiënten zonder diabetes schadelijker is dan bij patiënten met diabetes. Een glucose van 4.9 mmol/L bleek gerelateerd aan overlijden bij de patiënten zonder diabetes terwijl een veel lagere grenswaarde (3.5-3.9 mmol/L) werd gevonden bij patiënten met diabetes. Deze resultaten hebben belangrijke klinische implicaties. Ernstige hypoglycemie moet bij alle intensive care patiënten vermeden worden. Patiënten met diabetes tolereren wellicht ruimere glucose

streefwaarden, terwijl het vermijden van zowel ernstige als milde hypoglycemie, hyperglycemia als hoge glucose variabiliteit bij patiënten zonder diabetes erg belangrijk is.

In **Hoofdstuk 4** hebben we patiënt- en opnamegerelateerde karakteristieken van type 1 en type 2 diabetes patiënten opgenomen op een intensive care afdeling met elkaar vergeleken en onderzochten we de mate van glucoseregulatie. Van de diabetes patiënten die opgenomen werden op de intensive care classificeerden we 2% (n=27) als type 1 diabetes en 98% (n = 1547) als type 2 diabetes. De type 1 diabetes patiënten waren jonger, hadden een lagere BMI en werden vaker opgenomen op de intensive care vanaf niet-chirurgische afdelingen. De glucoseregulatie tussen de groepen bleek vergelijkbaar. Alleen de glucose variabiliteit bleek hoger te zijn bij de type 1 diabetes patiënten. Of het type diabetes ook invloed heeft op de relatie tot dysglycemie en de kans op overlijden dient onderzocht te worden in een grotere groep type 1 en type 2 diabetes patiënten.

Hoofdstuk 5 beschrijft de resultaten van een gerandomiseerde studie naar de veiligheid en effectiviteit van het gebruik van een onderhuidse (subcutane) continue glucose monitor (CGM) om glucoseregulatie te sturen bij intensive care patiënten. Tevens werd de werklast van IC verpleegkundigen en de dagelijkse kosten voor glucoseregulatie berekend. Alle 177 geincludeerde patiënten kregen een subcutane CGM. In de controlegroep werd reguliere glucoseregulatie verricht door middel van het uitvoeren van intermitterende glucosemetingen. Deze metingen werden ingevoerd in een glucose algoritme dat de insulineaanpassing en het volgende moment van meten aangeeft. Data van de CGM werden in de controlegroep geblindeerd. In de interventiegroep werden de data van de CGM ingevoerd in het bestaande glucose algoritme en werden geen intermitterende glucosemetingen verricht. Het gebruik van CGM om insulinebehandeling te sturen op de intensive care bleek even veilig (een gelijke incidentie van hypoglycemie) en effectief (een gelijk percentage glucosewaarden binnen de glucose streefwaarden) als de conventionele manier (intermitterende glucose metingen). Wel bleek er een significante reductie te zijn in werklast voor IC verpleegkundigen en in dagelijkse kosten voor glucose regulatie. Deze resultaten zijn een belangrijke stap voorwaarts in de ontwikkeling van een geautomatiseerd closed-loop glucose controle systeem.

In **Hoofdstuk 6** wordt de nauwkeurigheid vergeleken van twee verschillende continue glucose monitors (CGM): een invasieve CGM die door middel van fluorescentie intra-arterieel glucose meet (GluCath) en een minder invasieve subcutane CGM (Freestyle Navigator). Hoewel van te voren werd verondersteld dat het intra-arterieel meten van glucose nauwkeuriger zou zijn, bleek de minder invasieve subcutane CGM even nauwkeurig als de intra-arteriële CGM. De suboptimale prestatie van de intra-arteriële CGM werd onder meer gewijd aan signaalverlies tijdens patiëntactiviteit, suboptimale bevestiging en mogelijk interferentie met medicatie. Verbeteringen in sensortechnologie en

in nauwkeurigheid zijn nodig om CGM apparatuur veilig en gemakkelijk toe te passen op een intensive care.

Door de toegenomen beschikbaarheid van continue glucose monitoren zou het kwantificeren van glucose variabiliteit gemakkelijker moeten worden. Een veel gebruikte, maar ook veel bekritiseerde maat voor glucose variabiliteit is de gemiddelde amplitude van de glycemische excursies, oftewel MAGE. Het berekenen van MAGE is complex en oorspronkelijk werd voor het berekenen van MAGE potlood en lineaal gebruikt. Tegenwoordig zijn er ook geautomatiseerde computerprogramma's beschikbaar om de MAGE te berekenen. Deze programma's worden in **Hoofdstuk 7** met elkaar vergeleken. Bij eenzelfde CGM reeks bleken de computerprogramma's echter niet uniform een MAGE te berekenen. Dit impliceert dat het gebruik van een computerprogramma om een MAGE te berekenen van beperkte waarde is. Een minder complexe maat voor glucose variabiliteit lijkt de oplossing.

De laatste twee hoofdstukken richten zich op de gevolgen van stressgeïnduceerde hyperglycemie in relatie tot het stollingssysteem. Er is toenemend bewijs dat zowel chronische als acute hyperglycemie een verhoogde stollingsneiging geeft, wat zich uit in het vóórkomen van trombose. Er is echter nog niet opgehelderd wat de bijkomstigheid van hyperglycemie tijdens een trombo-embolie verklaart. Hyperglycemie kan zowel een resultaat zijn van de stressrespons van de trombo-embolie zelf, of het kan mogelijk een al langer bestaande gestoorde glucosetolerantie weergeven. Als hyperglycemie alleen een uiting is van gestoorde glucosetolerantie zou de diabetesincidentie in de jaren na een diagnose van trombose verhoogd moeten zijn. In **Hoofdstuk 8** testten we de hypothese dat het risico op het krijgen van diabetes na een longembolie verhoogd is. Daarvoor vergeleken we de incidentie van diabetes in twee verschillende groepen: mensen met en zonder een doorgemaakte longembolie. De resultaten lieten een vergelijkbare diabetesincidentie zien tussen de twee groepen, wat suggereert dat patiënten met een longembolie over het algemeen geen vergroot risico hebben op het ontwikkelen van diabetes en dat screening op diabetes in deze patiëntenpopulatie niet nodig is. Hyperglycemie tijdens een trombo-embolie is hoogstwaarschijnlijk voornamelijk stressgeïnduceerd door de trombo-embolie zelf.

Hyperglycemie kan ontstaan als gevolg van een operatie, bijvoorbeeld een orthopedische ingreep, en er is bewijs dat bij heupoperaties hyperglycemie ook bijdraagt aan de ontwikkeling van postoperatieve veneuze trombose. In **Hoofdstuk 9** wordt het effect van glucoseverlaging door middel van GLP-1 therapie op stollingsactivatie bij patiënten die een heupoperatie ondergaan beschreven. Bij 36 patiënten die een heupoperatie ondergingen werd een dubbelblind gerandomiseerde studie uitgevoerd waarin behandeld werd met het GLP-1 analoog liraglutide of placebo gedurende vier dagen. De resultaten lieten een

geringe daling in het gemiddelde glucose zien in de patiëntengroep behandeld met liraglutide. Deze geringe daling bleek echter geen invloed te hebben op de stollingsactivatie. Een causale relatie tussen glucoseverlaging en een veranderde stollingsactivatie kon in dit cohort van orthopedische patiënten niet worden bevestigd.

Slotopmerkingen

De onderzoeken gepresenteerd in dit proefschrift geven inzicht in de optimalisatie van glucoseregulatie van ziekenhuispatiënten. Zoals altijd roept ook dit onderzoek nieuwe vragen op. Ten eerste is een beter inzicht in de pathogenese van dysglycemie bij ziekenhuispatiënten noodzakelijk. Toekomstige studies zouden patiënten wellicht moeten classificeren naar hun pre-existente glycemische controle en naar de ernst van de glycemische verstoringen. Ten tweede moeten continue glucose monitors in de nabije toekomst worden verbeterd om van voordeel te kunnen zijn bij (ernstig zieke) patiënten. Betrouwbare en nauwkeurige apparaten zijn essentieel en kunnen als hulpmiddel van invloed zijn op klinische uitkomstmaten, zoals een verbeterde glucoseregulatie, minder hypoglycemische episodes en minder glucose variabiliteit. De ontwikkeling van een closed-loop glucose controle systeem voor de intensive care lijkt steeds meer binnen handbereik te komen. We kijken daarom ook uit naar de resultaten van een gerandomiseerd onderzoek, waarbij de haalbaarheid en effectiviteit van een geautomatiseerd closed-loop glucose controle systeem op basis van subcutane continue glucose metingen wordt onderzocht bij intensive care patiënten.

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Appendix

PHD PORTFOLIO

PhD Portfolio

Name: Marjolein Katinka Sechterberger
PhD period: July 2011-April 2015
Supervisor: J.B.L. Hoekstra
Co-supervisors: J.H. de Vries, P.H.J. van der Voort

Courses	Year	Ects
Basic Course Legislation and Organization for Clinical Researchers (BROK)	2011	0.9
Clinical epidemiology	2011	0.6
Practical Biostatistics	2012	1.1
Scientific Writing in English for Publication	2012	1.5
Clinical Data Management	2012	0.2
Clinical Epidemiology Schiermonnikoog (Boerhaave Committee, Leiden University Medical Center)	2013	2.5

Seminars, workshops and master classes		
Weekly department seminars Clinical Diabetology	2011-2015	3
Monthly department seminars Endocrinology	2011-2015	0.5
Master Class: 'responding to reviewers'comments'by dr. Gordon Guyatt	2012	0.5

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Oral presentations		
Glycaemic control and intensive care unit mortality: differences between patients with and without diabetes mellitus *Annual Meeting European Association for the Study of Diabetes, Berlijn, Duitsland* *North European Young Diabetologist Meeting, Noordwijk, Nederland*	2012	0.5
The incidence of diabetes mellitus following pulmonary embolism: a retrospective cohort study *Annual Dutch Diabetes Research Meeting, Oosterbeek, Nederland*	2012	0.5
Continuous glucose monitoring at the intensive care unit: nursing workload reduction and cost-benefit analysis *Annual Meeting European Association for the Study of Diabetes, Barcelona, Spanje*	2013	0.5
Controlling glucose during elective hip surgery to study the influence on coagulation *Investigator Initiated Study Dialogue Meeting, Kopenhagen, Denemarken*	2013	0.5

Poster presentations		
Continuous intra-arterial fluorescent glucose monitoring in post-operative cardiac surgery patients in the ICU: initial experience in the Netherlands *NVIC Nederlandse Intensivistendagen, Ede, Nederland*	2013	0.5

Poster presentations (continued)		
Poor agreement of computerized calculators to calculate the mean amplitude of glycaemic excursions *Annual Meeting European Association for the Study of Diabetes, Barcelona, Spanje*	2013	0.5
Intra-arterial versus subcutaneous continuous glucose monitoring in post-operative cardiac surgery patients in the ICU *International Conference on Advanced Technologies & Treatments for Diabetes, Wenen, Oostenrijk*	2014	0.5
(Inter)national conferences		
EASD Annual Meeting	2011-2014	4
ADDRM/NVDO Annual Meeting	2011-2014	2.5
NVDO Young Researchers Annual Meeting	2012	1
North European Young Diabetologist Meeting	2012	1
NVIC Nederlandse Intensivistendagen, Ede, Nederland	2013	0.2
Investigator Initiated Study Dialogue Meeting, Kopenhagen, Denemarken	2013	1
International Conference on Advanced Technologies & Treatments for Diabetes	2014-2015	1
Teaching		
Lectures		
Guest lecture at closed-loop glucose control meeting in Utrecht	2014	0.5
Tutoring		
Medical students during clinical observation work for a clinical study at the ICU	2013	0.5
Supervising		
A.J.E. Zonneveld, 'glucose variability and diabetes mellitus' bachelor thesis	2012	1
Y. Solomon, 'In-hospital use of GLP-analogues' bachelor thesis	2014	1
E.M. Boerboom, 'type I and II diabetes patients at the ICU' master thesis	2013-2014	1
Other		
Peer reviewer of two manuscripts of the Journal of Thrombosis and Haemostasis	2013	0.5

LIST OF PUBLICATIONS

List of Publications

Sechterberger MK, Siegelaar SE, DeVries JH. In-Hospital Hyperglycaemia: Quo Vadis?
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Sechterberger MK, Hutten BA, Hermanides J, Cohn DM, Hoekstra JB, Kamphuisen PW, DeVries JH. The incidence of diabetes mellitus following pulmonary embolism: a retrospective cohort study.
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Sechterberger MK, Bosman RJ, Oudemans-van Straaten HM, Siegelaar SE, Hermanides J, Hoekstra JB, De Vries JH. The effect of diabetes mellitus on the association between measures of glycaemic control and ICU mortality: a retrospective cohort study.
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Sechterberger MK, Luijf YM, Devries JH. Poor agreement of computerized calculators for mean amplitude of glycaemic excursions. Diabetes. *Technol Ther. 2014 Feb;16(2):72-5.*

Boom DT, Sechterberger MK, Rijkenberg S, Kreder S, Bosman RJ, Wester JPJ, Van Stijn I, DeVries JH, Van der Voort PHJ. Insulin treatment guided by subcutaneous continuous glucose monitoring compared to frequent point-of-care measurement in critically ill patients: a randomized controlled trial.
Critical Care 2014 Aug 20;18(4):453.

Sechterberger MK, van der Voort PHJ, Strasma P, DeVries JH. Accuracy of intra-arterial and subcutaneous continuous glucose monitoring in post-operative cardiac surgery patients in the ICU.
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Sechterberger MK, Hermanides J, Poolman RW, Kal JE, Meijers JCM, Hoekstra JBL, DeVries JH. Lowering blood glucose during hip surgery does not influence coagulation activation.
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DANKWOORD

Dankwoord

De totstandkoming van dit proefschrift was niet mogelijk geweest zonder hulp van vele mensen. Graag maak ik van de gelegenheid gebruik hen te bedanken.

Allereerst een woord van dank voor alle deelnemers aan de verschillende studies.

Joost, motivator en rolmodel: wat een feest om bij jou te mogen promoveren! Ik bewonder je enthousiasme over elk nieuw wetenschappelijk (of sociaal gerelateerd) idee, je optimisme, maar ook je betrokkenheid, en altijd kritische blik. Je betrokkenheid weerspiegelt zich in het feit dat je al heel snel (lees: na 10 dagen) met Hans op de bank zat om een blik op Emma te werpen! Ik heb veel van je werkattitude geleerd en wil je bedanken voor de fijne begeleiding. Staat het suikerpotje nog te 'shinen' of staat hij inmiddels ergens achterin een kast?!

Hans, eenvoud is het kenmerk van het geniale, iets wat ik helemaal bij jou vind passen. Zonder poespas, maar op uiterst strategische wijze ben jij uitgegroeid tot een belangrijke speler van het wetenschappelijk strijdtoneel. Je straalt plezier uit in de wetenschap, je bent scherp en kritisch en geeft uiterst toegewijde begeleiding. Als er uit jouw mond "Topperdepop" kwam dan wist ik dat het goed was! Dank voor het vertrouwen dat je in mij had en voor het aanleren van alle fijne kneepjes van het (onderzoeks)vak.

Peter, met veel plezier denk ik terug aan de vele momenten dat ik voor overleg bij je binnen wipte in het OLVG. Je bent een meester in het creëren van rust, ondanks de hectiek van de IC. Ik bewonder je positieve en ongecompliceerde instelling en je altijd vernieuwende ideeën. Niets is jou te gek. Ik ben erg vereerd dat je mijn copromotor bent!

Graag bedank ik prof. dr. Fliers, prof. dr. Romijn, prof. dr. Büller, prof. dr. Bilo, prof. dr. Oudemans-van Straaten en prof. dr. Bakker voor het beoordelen van mijn proefschrift en hun bereidheid zitting te nemen in mijn promotiecommissie.

Mijn promotie kenmerkte zich door een multidisciplinaire samenwerking van verschillende afdelingen van het OLVG. Een woord van dank aan hen is hier daarom zeker op zijn plaats.

De IC-afdeling, de medische staf, verpleging en ondersteunend personeel. Dank voor het mogelijk maken van het intensieve sensor onderzoek. De Amerikaanse manier van onderzoek doen waren jullie niet gewend, maar ondanks dat hielden jullie je hoofd koel, dank daarvoor! In het bijzonder dank ik Saskia Rijkenberg voor haar praktische adviezen, Wim Togni voor zijn technische ondersteuning en Addy Bianchi voor alle ICT-technische tips and tricks. Rob Bosman, jouw wetenschappelijke interesse in combinatie met jouw passie voor ICT is iets unieks en dat heb ik met bewondering gade geslagen. Dank voor je opbouwende kritiek op mijn stukken en ik hoop echt dat het closed-loop glucose control project een succesvol gevolg gaat krijgen!

De afdeling orthopedie, in het bijzonder Rudolf Poolman en Vanessa Scholtes. Dank dat ik het vertrouwen kreeg mijn glucose-onderzoek op jullie afdeling uit te voeren.

De afdeling anesthesie, Jasper Kal, dank voor de prettige samenwerking tijdens het onderzoek en je betrokkenheid.

De medewerkers van het HKCL: vele uurtjes, vaak zelfs voor de werkdag begon, zat ik al bij jullie te pipetteren. Elly, dank voor al je praktische adviezen en fijn dat je altijd voor vragen beschikbaar was. Erna, altijd gezelligheid als jij er was! Ik heb genoten van je aanwezigheid. Maar ook alle andere dames van het lab, teveel om op te noemen, bedankt voor alle uurtjes vermaak!

Zeker niet te vergeten zijn alle medewerkers van **het stollingslab** van het AMC (in het bijzonder Joost, Wil en Lucy). Dank voor jullie gastvrijheid en het mogelijk maken van de analyses. Tevens alle **co-auteurs** op de verschillende publicaties. Dank voor jullie enthousiasme en kritische blik.

Collegae promovendi, Anne, Yoeri, Josefine, Arianne, Sil, Wanda, Airin: ik kwam terecht in een warm onderzoeksnest waar ik me al snel thuis voelde! Dank voor de introductie binnen het onderzoeksbestaan en voor alle gezellige koffie- en lunchuurtjes.

Roomies, Wanda, Airin, en later Lonneke. Wat een heerlijke sfeer hing er altijd op onze kamer. **Wan**, wat heb ik veel om jou gelachen, wat ben je toch een heerlijk mens! Ik heb je erg gemist toen je het diabetesnest ging verlaten. **Airin,** klein van stuk, maar wat een sterke persoonlijkheid! Dank voor je luisterend oor en je goede adviezen als ik ergens onzeker over was. **Lon,** mijn rechter vleugel, wat bewonder ik je gedrevenheid en doorzettingsvermogen. Ik weet zeker dat je het nog ver gaat schoppen binnen de interne.

Oudpromovendi, Sanne, Bregtje, Jeroen, Sarah, Iris, Titia, Aline, Max, dank voor de gezelligheid op de EASD-reizen en de dinertjes! Sarah en Jeroen, heel erg bedankt dat ik op jullie ‘stress-hyperglycemie-onderzoekstrein’ mocht stappen!

Nieuwe aanwinsten, Pieter, Jort, Helga, Lonneke en Sigrid: de diabetesgroep leeft voort en hoe! Dank voor de gezellige tijd aan het eind van mijn promotie!

Frits, onmisbaar in de diabetesgroep vanwege je hoge mate van creativiteit en vernieuwende wetenschappelijke ideeën. Dank voor de fijne samenwerking. **Karin,** je stond altijd voor me klaar en je was een held in het regelen van vele zaken. Dank voor al je hulp!

Studenten van het sensorproject: dank voor de vele uurtjes dat jullie elke armbeweging van een patiënt observeerden! Suzanne en Daphne, wat een werk hebben jullie verricht, zowel op de werkvloer als achter de computer, dank voor alles! Esther, het nazoeken van type 1 diabetes patiënten in de database bleek een monsterproject. Maar jij hield vol. Erg veel dank daarvoor!

Mijn paranimfen, Willemijn en Annemiek. **Willie,** ik heb niet eerder iemand ontmoet die zo eerlijk en echt is zoals jij. Al jaren delen we lief en leed, onder het genot van een fietstochtje, een yoga-zitting, of een theetje of biertje. Dank dat je mijn paranimf wilt zijn! **Miek,** warm, enthousiast en altijd energie voor tien. Altijd sta je voor me klaar. Wat ben ik ontzettend blij met jou als vriendin en nu als paranimf!

Luite, veel dank voor het mooie ontwerp van de voorkant van mijn proefschrift!

Vrienden, te veel om op te noemen, af en toe even helemaal los gaan op een feestje is heerlijk! Dank voor jullie belangstelling, alle gezelligheid en leuke avondjes!

Schoonfamilie, Hermine, Shimon, Sanne, Tim en Omri, al vanaf het begin voelde ik me ontzettend thuis in jullie gezin. Jullie open houding en humor waardeer ik ontzettend. Hoewel ik nog nooit van Kropswolde had gehoord kom ik nu ontzettend graag naar het Groningse platteland: het geeft me rust en ruimte. Dank voor alle fijne en gezellige momenten en jullie steun en zorgen voor Emma!

Zusjes, Rijk en An. De laatste jaren waren in alle opzichten turbulent. Vele mooie en enkele verdrietige gebeurtenissen, veel buitenland-avonturen, maar toch zorgden we ervoor dat we elkaar niet uit het oog verloren. **Rijkie,** voor ons is één blik genoeg! Je bent ontzettend belangrijk voor me en hoop nog heel veel leuke avonturen met je te beleven! Dank voor alle peptalks, zeker bij het afronden van mijn proefschrift. **An,** of het nou Australië is of de bush van Zuid-Afrika, niets is jou te gek. Ik bewonder je doorzettingsvermogen en positieve blik en ben enorm trots op hoe je het allemaal doet. Tevens ben jij de meest enthousiaste tante ter wereld die ik me kan bedenken: heerlijk hoe jij van Emma kan genieten!

Pappa, ik ben in jouw voetsporen getreden als arts en daar ben ik erg trots op! Ik wil je bedanken voor het grenzeloos vertrouwen dat je in mij hebt. Je hebt me nieuwsgierigheid, discipline en zelfvertrouwen bijgebracht: onmisbare eigenschappen in het leven. Je bent een enorme steun voor me en staat, nu samen met Wil, altijd voor me klaar. Dank je wel!

Mamma, plotseling verliet je ons. Een enorm verlies en ik mis je nog iedere dag. Wat zou je trots geweest zijn en genoten hebben van weer een bijzondere mijlpaal: mijn promotie! Jij hebt mij als geen ander geleerd wat humor, toewijding en genieten is: jouw positivisme leeft in mij voort!

Lieve **Bram,** nooit gedacht dat een spontaan (beschonken) dansje met jou op het KEI Eindfeest tot zoiets moois kon uitgroeien! Met jou voel ik me helemaal compleet: you rock my world! Dank voor je onvoorwaardelijke steun, in alle opzichten. Ik verheug me op al het moois wat komen gaat!

Tot slot, lieve **Emma,** mijn kleine poppedijne, ineens was jij er! Het allermooiste wat me is overkomen. Je zonnige lach doet al het andere vervagen en betovert mij iedere dag weer!

CURRICULUM VITAE

Curriculum Vitae

Marjolein Katinka Sechterberger werd op 4 juni 1984 als jongste telg van het gezin geboren te Doetinchem en groeide op in de Achterhoek. In 2002 behaalde zij haar gymnasium diploma aan het St. Ludger College in Doetinchem, waarna zij voor een half jaar vertrok naar Barcelona om zich de Spaanse taal meester te maken. Marjolein begon in september 2003 aan haar studie geneeskunde aan de Rijksuniversiteit Groningen. De studententijd in Groningen was geweldig; de jaren vlogen om. Tussendoor onderbrak zij haar studie een half jaar om de aanhoudende reiskriebels te stillen met vrijwilligerswerk in een Argentijns ziekenhuis. Na de daaropvolgende reis door Latijns Amerika vervolgde Marjolein haar studie en ging zij coschappen lopen in het Deventer Ziekenhuis, waar haar interesse in de inwendige geneeskunde ontstond. In Deventer leerde zij ook haar geliefde Bram kennen, die pardoes op de stoep stond tijdens haar tropenstage in Suriname. Liefde kent geen grenzen.

Na het afronden van haar studie in 2010 begon Marjolein als ANIOS interne geneeskunde in het Westfries Gasthuis te Hoorn. Een in juli 2011 op een presenteerblaadje aangereikt promotieonderzoek op de afdeling inwendige geneeskunde van het AMC te Amsterdam greep zij met beide handen aan. Onder leiding van prof. dr. Joost Hoekstra, dr. Hans de Vries en prof. dr. Peter van der Voort heeft dit traject geleid tot het voor u liggende proefschrift. Promoveren is goed bevallen: daar kan dochter Emma (steeds beter verstaanbaar) over meepraten!

Per 1 april 2015 is Marjolein begonnen met de opleiding tot internist in het Onze Lieve Vrouwe Gasthuis te Amsterdam. De vrije uurtjes brengt zij graag door met de liefdes van haar leven, in de tuin van hun heerlijke huis in Amsterdam-Oost.