Measure for measure: consequences, detection and treatment of hyperglycaemia
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“Pissing Evil”

That is how sir Thomas Willis in the 17th century described the high concentrations of glucose found in the urine of patients. The sweet urine described by dr. Willis was the result of pathologically elevated concentrations of glucose in the blood called hyperglycaemia. In those days, hyperglycaemia would eventually mean certain death. Since then we have come a long way, but are still left with questions on the consequences of hyperglycaemia and how we best measure it in order to take the appropriate measures. In this thesis, several studies are presented that investigated the consequences, detection and treatment of hyperglycaemia.
Measure for Measure

Consequences, Detection and Treatment of Hyperglycaemia

Jeroen Hermanides
Measure for Measure

Consequences, Detection and Treatment of Hyperglycaemia

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Jeroen Hermanides

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# TABLE OF CONTENTS

<table>
<thead>
<tr>
<th>Chapter</th>
<th>Title</th>
<th>Page</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Introduction</td>
<td>7</td>
</tr>
<tr>
<td><strong>PART I Consequences of Hyperglycaemia</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>2</td>
<td>Glucose: a prothrombotic factor?</td>
<td>15</td>
</tr>
<tr>
<td>3</td>
<td>Venous thrombosis is associated with hyperglycaemia at diagnosis: a case–control study</td>
<td>31</td>
</tr>
<tr>
<td>4</td>
<td>Hip surgery sequentially induces stress hyperglycaemia and activates coagulation</td>
<td>43</td>
</tr>
<tr>
<td>5</td>
<td>Stress-induced hyperglycaemia and venous thromboembolism following total hip or total knee arthroplasty</td>
<td>53</td>
</tr>
<tr>
<td>6</td>
<td>Early postoperative hyperglycaemia is associated with postoperative complications after pancreatoduodenectomy</td>
<td>67</td>
</tr>
<tr>
<td><strong>PART II Detection and Treatment of Hyperglycaemia</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>7</td>
<td>Sense and nonsense in sensors</td>
<td>87</td>
</tr>
<tr>
<td>8</td>
<td>Sensor augmented pump therapy lowers HbA1c in suboptimally controlled type 1 diabetes; a randomised controlled trial</td>
<td>97</td>
</tr>
<tr>
<td>9</td>
<td>Sensor augmented insulin pump therapy to treat hyperglycaemia at the coronary care unit; a randomised clinical pilot trial</td>
<td>117</td>
</tr>
<tr>
<td>10</td>
<td>No apparent local effect of insulin on microdialysis continuous glucose-monitoring measurements.</td>
<td>133</td>
</tr>
</tbody>
</table>
Chapter 11  Algorithm to treat postprandial glycaemic excursions using a closed-loop format: a pilot study 141

Chapter 12  Glucose variability is associated with ICU mortality 151

Chapter 13  Hypoglycaemia is associated with ICU mortality 165

Chapter 14  Mean glucose during ICU admission is related to mortality by a U-shaped curve; implications for clinical care 179

Chapter 15  Summary and future considerations 197
Samenvatting en toekomstperspectief 205
List of publications 213
Biografie 217
Co-authors 221
Dankwoord 225
Introduction

J Hermanides
“Pissing Evil”

That is how sir Thomas Willis, the famous London physician, described the high concentrations of glucose found in the urine of his patients.\(^1\) For this, the underlying illness became known as “diabetes mellitus”, translated as “flowing sweetness”. The sweet urine described by dr. Willis was the result of pathologically elevated concentrations of glucose in the blood called hyperglycaemia. With no treatment available at that time, patients with hyperglycaemia would eventually face certain death. Nowadays in the Western world insulin and other glucose lowering agents have become available to treat hyperglycaemia and life expectancy of patients with diabetes continues to increase.\(^2\) However, patients with diabetes mellitus type 1 still face intensive, bothersome and lifelong treatment, trying to prevent complications.\(^3;4\) Recently the growing epidemic of diabetes mellitus type 2 has put this form of diabetes in the spotlight.\(^5\) Even more since morbidity and mortality are worrying.\(^6\)

In 2001 another form of hyperglycaemia drew everyone’s attention (at least in the medical world) when Greet van den Berghe in Leuven showed that strict glycaemic control in the Intensive Care Unit (ICU) reduced mortality by a relative 43\%.\(^7\) Especially patients without known diabetes, but with transient hyperglycaemia because of severe illness, benefitted from this intervention.\(^8\) This so-called “diabetes of injury” or “stress-hyperglycaemia” turned out to be a risk factor for poor outcome in a variety of acute- and severe illnesses.\(^9;10\)

But what exactly is the harm of hyperglycaemia? It is known to cause micro-, macrovascular and neural damage in longstanding diabetes.\(^3;4;6\) Another major cause of morbidity and mortality is the influence of hyperglycaemia on the coagulation system, thereby causing arterial and venous thrombosis, leading to stroke, myocardial infarction and pulmonary embolism. The consequences of stress hyperglycaemia in different patient groups remain unclear. In general it is thought to have its impact on the immune system, the endothelium and the coagulation system.\(^9\) The exact effects seem to vary between patient groups and many research questions remain unanswered. In **PART I** of this thesis the effects of hyperglycaemia on the coagulation system are investigated in venous thrombosis and after orthopaedic surgery. **Chapter 2** gives a review of the current evidence on hyperglycaemia and thrombosis. The association between venous thrombosis and hyperglycaemia is investigated in **Chapter 3**, whereas **Chapter 4** and **5** study the influence of orthopaedic surgery on glucose metabolism, coagulation activation and
postoperative venous thrombosis. Furthermore, the consequences of hyperglycaemia after pancreatoduodenectomy are studied in Chapter 6.

With developing technologies, new possibilities have become available to target hyperglycaemia. After advancing from bulky insulin needles to the delicate pens today, the development of the insulin pump made it possible to continuously administer and adjust insulin administration.12 This flexible insulin dosing proved beneficial in treating diabetes mellitus.13 Hereafter, new ways of measuring glucose became available with the continuous glucose sensors. Instead of the snapshot glucose values gained with fingerstick measurements, there was now a continuous stream of data available.14 Only recently, these two devices have been combined in one integrated sensor augmented insulin pump15, a major step towards the development of a closed-loop system or artificial pancreas. Clearly, the detection and treatment of hyperglycaemia is being modernised and provides a source for interesting research questions in PART II.

Chapter 7 comments on the development of the glucose sensors so far. In Chapter 8 the results of a randomised controlled trial investigating the efficacy of sensor augmented pump therapy are presented. In Chapter 9 the application of sensor augmented pump therapy in patients with acute myocardial infarction and hyperglycaemia is studied. Also further steps towards the closed-loop system have been studied and described by infusing insulin in the close proximity of subcutaneous glucose sensors in Chapter 10 and the development of a closed-loop algorithm in Chapter 11.

After the first Leuven study by Greet van den Berghe, following trials could not reproduce her impressive results. Even more, the evidence from the recent NICE-SUGAR study implies that strict glycaemic control in the ICU does more harm than good.16 Whether or not strict glycaemic control in the ICU should be common practice and what guidelines to follow is being heavily debated. Factors not yet studied could be involved and explain the differences between the trials. We therefore used a different approach in measuring hyperglycaemia, by taking glucose variability into account, which is done in Chapter 12. A major side effect of treating hyperglycaemia and important factor in interpreting study results is hypoglycaemia. The consequence of hypoglycaemia in the ICU has been investigated in Chapter 13. Finally, the implications for clinical care resulting from our data and the Leuven and NICE-SUGAR trials are discussed in Chapter 14.

The title of this thesis refers to the Shakespeare play “Measure for Measure”, which means that every action is followed by a reaction or every upside has its downside. As with Shakespeare’s play, this thesis is about searching for “truths” and
questioning methods of *measuring* as these will directly influence the *measures* that are taken. The bad guy in this thesis is however not a harsh judge from ancient Vienna named Angelo, but a pathological phenomenon called hyperglycaemia.
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CONSEQUENCES OF HYPERGLYCAEMIA
Glucose: a prothrombotic factor?

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Submitted for publication
ABSTRACT

Evidence is mounting that both diabetes and stress induced hyperglycaemia contribute to coagulation activation and hypofibrinolysis, resulting in a procoagulant state that predisposes patients to thrombotic events. Hyperglycaemia is often accompanied by hyperinsulinaemia and their combined effects may be even stronger. In this review we discuss the current evidence regarding the role of glucose as prothrombotic factor, not only in relation to diabetes, but also with regard to acute hyperglycaemia. Furthermore, the effects of glucose lowering therapies to prevent hypercoagulability are considered.
INTRODUCTION

Patients with diabetes are notorious for their risk of vascular events. Apart from the effects of diabetes and its prerequisite hyperglycaemia on the development of atherosclerosis, this high risk may also be caused by the procoagulant state found in diabetes.\textsuperscript{1,2}

In recent years hyperglycaemia per se, even without overt diabetes, has gained interest as a potential target to improve clinical outcomes in hospitalised patients with acute illness.\textsuperscript{3} In this setting the effects of hyperglycaemia on the coagulation system may be of greater importance than previously considered. Here we discuss the current evidence regarding potentially harmful changes in the coagulation system and subsequent risk of thrombotic disease, not only caused by diabetes but also by acute hyperglycaemia.

CHRONIC HYPERGLYCAEMIA

Type 2 diabetes

Type 2 diabetes (DM2) is defined by hyperglycaemia, but often accompanied by hyperinsulinaemia, dyslipidaemia, hypertension and obesity. Its effects on the coagulation system can therefore not easily be attributed to either one of these entities\textsuperscript{4}, but the impact of glucose on coagulation in diabetes has been studied extensively.

Markers of fibrinolysis and coagulation

Both parameters of increased coagulability as well as a fibrinolytic impairment have been found in DM2, although there are many different markers in the circulation to measure these abnormalities. Platelet-dependent thrombin generation, for instance, was measured in patients with poor glycaemic control, good glycaemic control and healthy controls. In vitro induced thrombin generation was found to be increased in platelet-rich plasma from diabetes patients compared to healthy controls and a significant elevation of thrombin levels was also demonstrated in plasma from poorly controlled DM2 when compared to well controlled patients.\textsuperscript{5} In a placebo controlled trial using troglitazone combined with diet modification a significant association was shown between improved glycaemic control and blood thrombogenicity as reflected by a reduction in ex-vivo thrombus formation in a Badimon perfusion chamber. Improved glycaemic control was the only significant predictor of a decrease in blood thrombogenicity irrespective of
In a group of poorly controlled DM2 patients (HbA1c 10%), extraordinarily high concentrations of plasminogen activator inhibitor-1 (PAI-1), indicating hypofibrinolysis, were detected leading the authors to conclude that profound hyperglycaemia is accompanied by profound increases in PAI-1. Subsequent treatment of hyperglycaemia by either glipizide or metformine as monotherapy comparably decreased PAI-1, which argues for an effect of glucose lowering rather than a specific medication effect. This state of hypofibrinolysis was recently confirmed in a case-control study; patients with DM2 were found to have a prolonged clot lysis time as well as elevated levels of PAI-1 and von Willebrand factor (vWF). The impairment in the fibrinolytic system in DM2 of interest since these impairments are independent primary risk factors for myocardial infarction. In addition to hypofibrinolysis, the levels of prothrombin fragment 1+2 (F1+2) were also found to be associated with the presence of proven cardiovascular disease in DM2 patients.

**Hyperinsulinaemia**

To disentangle the effects of glucose and insulin in type 2 diabetes, Boden et al studied the effects of acute correction of hyperglycaemia with insulin followed by either 24 hours of experimentally induced normoinsulinaemic euglycaemia, 24 hours of euglycaemic hyperinsulinemia or 24 hours of combined hyperinsulinaemia and hyperglycaemia, in DM2 patients as well as healthy controls. They found baseline elevations of tissue factor procoagulant activity (TF-PCA), monocyte TF mRNA and plasma factor VII, factor VIII and thrombin-antithrombin (TAT) complexes in patients with DM2 compared to healthy controls. Normalizing glucose significantly decreased TF-PCA. Increasing insulin levels raised TF-PCA and elevating glucose and insulin levels together resulted in a much larger rise of TF-PCA, which was associated with increases in TAT and F1+2. Thus glucose and insulin both seem to play a role in the pathogenesis of the prothrombotic state in type 2 diabetes.

**Effect of glucose lowering therapies**

The effects of improved glycaemic control on PAI-1 levels in DM2 have been demonstrated for different oral antidiabetic therapies, such as metformin alone or in combination with pioglitazone or rosiglitazone and glimepiride in combination with pioglitazone or rosiglitazone. Metformin, which already had proven beneficial cardiovascular effects in the United Kingdom Prospective Diabetes Study trial, also reduced factor VII and fibrinogen levels and shortened clot lysis time. When metformin was added to a sulphonylurea derivate in poorly controlled elderly
DM2 patients, the resulting substantial improvement in glycaemic control was accompanied by beneficial changes in markers of platelet function (platelet factor 4 and beta-thromboglobulin), thrombin generation (fibrinopeptide A, F1+2, and D-dimer) and fibrinolysis (PAI-1 activity and antigen). In the Diabetes Prevention Program, which studied the stages preceding diabetes, i.e. impaired glucose tolerance, lifestyle interventions even more than metformin treatment showed a modest, but significant, amelioration in fibrinogen levels. Data on the effects of insulin therapy on coagulation and fibrinolysis markers in DM2 are scarce, and more conflicting than for the oral antidiabetic treatments. Although some authors report beneficial effects of insulin, others were unable to find improvements with insulin therapy.

Type 1 Diabetes

Markers of fibrinolysis and coagulation
In type 1 diabetes (DM1) patients the specific contribution of hyperglycaemia to the prothrombotic state is clearer as they lack the other risk factors which confound the relationship in DM2 patients. In a long term follow up study, a highly significant correlation was found between mean HbA1c in DM1 patients over the course of 18 years and impaired fibrinolysis as represented by elevated PAI-1 and decreased tissue plasminogen activator (t-PA). In a smaller setting, eight DM1 patients on continuous subcutaneous insulin infusion therapy were withheld treatment for the duration of four hours which caused a rise of PAI-1 and plasma TF. Although the authors conclude that early ketogenesis causes a prothrombotic change in DM1 patients, the effects of acute hyperglycaemia in this setting cannot be excluded. Platelet function tests, including aggregation and platelet adhesion tests, did not improve with intensive glycaemic control in DM1. However, platelet function tests are notoriously variable and the authors may not have included a sufficient number of patients to overcome this disadvantage. Finally, despite the abundant evidence of fibrinolytic impairment in diabetes, not all markers of fibrinolysis are abnormal. Thrombin-activatable fibrinolysis inhibitor (TAFI) for instance, showed no difference between patients with DM1 and healthy controls a finding which was recently confirmed in DM2 patients.

Diabetes and thrombosis
DM2 and, maybe to a lesser extent, DM1 are known for a high risk of developing atherothrombotic events. This is at least partly explained by hyperglycaemia, given
the continuous relationship between the development of cardiovascular disease and glycaemic control, also in DM2. Moreover, intensive blood glucose control in the early stages of the disease proved effective in lowering the long term incidence of cardiovascular disease in both disease entities. Recently it has become clear that not only atherothrombotic events are seen more often in patients with diabetes but that venous thromboembolism (VTE) is also more frequent in this patient group. Movahed found an odds ratio (OR) of 1.27 (95% CI 1.19 to 1.35) for the occurrence of pulmonary embolism in DM patients. Earlier, Tsai et al also found diabetes to be a risk factor for VTE with a hazard ratio (HR) of 1.46 (95% CI 1.03 to 2.05), even after adjusting for BMI, a known predictor of VTE. A recent meta-analysis on cardiovascular risk factors for VTE showed DM to be an independent risk factor with an OR of 1.41 (95% CI 1.12 to 1.77). Although the effect of glucose lowering on VTE risk remains to be established, the overrepresentation of both venous as well as atherothrombosis in diabetes is highly suggestive of a prothrombotic effect of its main component, hyperglycaemia, in addition to its more established effects on atherosclerosis.

ACUTE HYPERGLYCAEMIA

Apart from chronic hyperglycaemia, it is important to consider the role of acute hyperglycaemia. Frequently, this is transient hyperglycaemia resulting from metabolic deterioration during (severe) illness. Although this may result from pre-existing and undiagnosed diabetes, 30-40% of patients with “stress-hyperglycaemia” will revert to normoglycaemia with follow-up. Transient hyperglycaemia will usually be accompanied by transient hyperinsulinaemia.

**Markers of fibrinolysis and coagulation**

The effect of hyperglycaemia and hyperinsulinaemia on the coagulation system in subjects without diabetes has been studied rather extensively. Already in 1988, Ceriello showed that experimentally increased glucose levels activated the coagulation system in non-diabetic subjects by increasing factor VII. Stegenga and co-workers demonstrated in healthy volunteers that hyperglycaemia (12 mmol/l), irrespective of insulin levels, activates coagulation, marked by an increase in TAT complexes and soluble tissue factor (sTF). In contrast, hyperinsulinaemia inhibited fibrinolysis by increasing PAI-1 levels. This was even more profound when systemic inflammation was induced. In vitro, studies with endothelial cells from pig aortas exposed to increasing glucose concentrations indicated that PAI-1
secretion and synthesis increased in parallel to glucose levels. Activation of the tissue factor pathway following induction of hyperglycaemia in healthy volunteers was also observed in by Rao and colleagues. In a subsequent study, 29 healthy volunteers were exposed to combinations of euglycaemia or hyperglycaemia with normoinsulinaemia or hyperinsulinaemia. They found that selective hyperglycaemia and hyperinsulinaemia activated the coagulation system, but the combination of both showed the largest increase in sTF procoagulant activity, TF expression on monocytes and TF mRNA in monocytes, TAT, factor VII, factor VIII and platelet activation, measured by platelet expression of soluble CD40 ligand. Finally, Nieuwdorp and co-workers discovered that hyperglycaemia in healthy volunteers concomitantly reduced the protective glycocalyx of the endothelium and the function of the endothelium itself and increased prothrombin fragment 1+2 and D-dimer levels.

**Acute hyperglycaemia and coagulation in the ICU**

Two studies have attempted to elucidate the role of the coagulation system in relation to strict glycaemic control. In the first Leuven trial, van den Berghe successfully implemented strict glycaemic control in the ICU, showing a clear mortality benefit. She published a subanalysis, investigating the effect of strict glucose control on coagulation and fibrinolysis. Although a variety of parameters was assessed, no differences were found between the intensively treated group and the control group. However, samples were obtained only at 5 and 10 days after admission and an acute effect within the first 5 days could have been missed. Savioli and coworkers investigated the effect of strict glucose control on coagulation and fibrinolysis in patients with septic shock on admission and up to 28 days after admission. They found that strict glucose control reduced the impairment of the fibrinolytic system, as measured by PAI-1. However, strict glucose control in the ICU is now being heavily debated because of the recently published NICE-SUGAR trial, which showed increased mortality in the intervention group.

**Acute hyperglycaemia and thrombosis**

Several thrombotic conditions are associated with acute hyperglycaemia, most importantly myocardial infarction (MI), stroke and venous thromboembolism (VTE). During MI, admission hyperglycaemia predicts morbidity and mortality in patients without previously diagnosed diabetes. Furthermore, elevated admission glucose levels are directly related to the infarct size and reductions in coronary flow
after stent implantation in non-diabetic patients.\textsuperscript{48,49} This might be related to intravascular thrombotic events. Patients with acute coronary syndrome and admission glucose >7.0 mmol/l had elevated values of thrombin-antithrombin complexes and platelets activation, measured by soluble CD40 ligand levels, as compared to patients admitted with glucose <7.0 mmol/l.\textsuperscript{50} Also the fibrin clot lysis time was impaired in hyperglycaemic subjects. In another study activation of platelets, as measured by beta-thromboglobulin, was associated with hyperglycaemia after MI, independent of pre-existing diabetes.\textsuperscript{51} In a rabbit model, reducing hyperglycaemia using acarbose resulted in decreased infarct size.\textsuperscript{52}

In stroke patients, admission hyperglycaemia was related to the infarct size\textsuperscript{53-55} and a strong predictor of post-stroke morbidity and mortality.\textsuperscript{56,57} Ribo and colleagues showed that acute but not chronic hyperglycaemia during stroke was associated with lower tissue-type plasminogen activator recanalization rates, suggesting an impairment of the fibrinolytic system by hyperglycaemia.\textsuperscript{58}

A few studies investigated the relation between venous thromboembolism (VTE) and hyperglycaemia. Pre-surgery hyperglycaemia (>11.1 mmol/l) is associated with an OR of 3.2 for pulmonary embolism after orthopaedic surgery.\textsuperscript{59} However, this might reflect undiagnosed and uncontrolled diabetes. Recently, we published data on glucose levels at presentation for suspected VTE and showed that higher glucose levels at presentation are associated with actually having VTE, in a clear dose-response fashion.\textsuperscript{60} During hip surgery, glucose levels rise in patients without diabetes and this precedes a rise in factor VIII, vWF and F1+2\textsuperscript{61}, but whether this is a causal relation needs further investigation.

Unfortunately, clinical trials in patients with MI and stroke have not been able to reach their targets and trials aiming to prevent VTE are awaited. After proven beneficial in patients with DM in the DIGAMI study, the value of glucose-insulin-potassium (GIK) infusion on outcome after MI in patients without diabetes was investigated, but no significant contrast in glucose control between the intervention and control groups was achieved,\textsuperscript{62-65} The GIST-UK trial randomised stroke patients to GIK infusion or saline infusion to investigate the effect of glucose modulation with GIK. In this trial no clinical benefit was observed, however the trial was underpowered and the glucose lowering effect of GIK was small and patients were treated for only 24 hours.\textsuperscript{66}
POSSIBLE MECHANISMS

Many theories on how hyperglycaemia leads to hypercoagulability have already been proposed and studied. First, on a cellular level, hyperglycaemia and also hyperinsulinaemia increases the expression of PAI-1 on vascular smooth muscle cells in vitro, thereby increasing its concentration and activity. As a result, the activity of t-PA is reduced thereby decreasing the fibrinolytic potential. The authors suggested that a direct effect of glucose and insulin on gene transcription could be responsible. Indeed, hyperglycaemia in the presence of insulin increases the activity of transcription factor nuclear factor kappa-B (NF-kB) in human hepatocyte cells and the gene transcription of PAI-1 in vitro, which suggests that PAI-1 transcription is increased via NF-kB. Because this effect disappeared when an antioxidant was added to the medium, hyperglycaemia-induced oxidative stress was hypothesised to be the major activator of NF-kB. Khechai and coworkers studied the effect of advanced glycation end products (AGE) on TF expression in human monocytes and concluded this AGE-induced TF expression at the mRNA level, which could be diminished by adding antioxidants. The effect of AGEs on coagulation activation was also seen when human umbilical vein endothelial cells were exposed to AGEs and AGEs dose-dependently increased procoagulant activity and TF levels. Withholding insulin in patients with DM1 increased TF and PAI-1 levels, which was accompanied by a rise in malondialdehyde (MDA) and protein carbonyl groups (PCG), both markers of oxidative stress.

Next, hyperglycaemia directly influences the vulnerability of the vascular endothelium by affecting the glyocalyx, a protective layer of proteoglycans covering the vessel wall. This results in enhanced platelet-endothelial cell adhesion and release of coagulation factors harboured within the endothelial glyocalyx. Finally, hyperglycaemia exerts its effects also extracellular by direct glycation of proteins involved in coagulation. Verkleij et al. showed that glycated TAFI looses its fibrinolytic properties in vitro, although this could not be reproduced in vivo. Fibrin clots from patients with diabetes type 2 are more dense as compared to controls and displayed an altered structure, resulting in longer clot lysis time. In vivo glycaemic control was directly correlated to the clot density from the patients. A likely explanation for this is the possible non-enzymatic glycation of fibrin. It is conceivable that other coagulation proteins are also glycated, altering their activity. Thus, multiple complex pathways are likely to be involved in the induction of hypercoagulability by hyperglycaemia, and its effect is more profound in combination with hyperinsulinaemia.
SUMMARY

In summary, the evidence is compelling that both chronic and acute hyperglycaemia contribute to coagulation activation and hypofibrinolysis, resulting in a procoagulant state that predisposes patients to thrombotic events (Figure 1). What is more, hyperglycaemia is often accompanied by hyperinsulinaemia and their combined effects may result in an even stronger hypercoagulable state. Although we separately discussed the effects of chronic and acute hyperglycaemia on coagulation, the current evidence gives no reason to assume that the underlying mechanisms differ.

Intensive glycaemic control in patients with diabetes reduces the incidence of thrombotic diseases such as myocardial infarction and stroke in the long run. Whether intensive glucose control during acute hyperglycaemia during acute MI, stroke and VTE could prevent hypercoagulability and thereby improve outcome awaits further investigation in randomised controlled trials.
Glucose: a prothrombotic factor?

Figure 1- A simplified impression of the relations between hyperglycaemia, hyperinsulinaemia and coagulation, leading to clinical outcome.
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Glucose: a prothrombotic factor?


Chapter 2


Venous thrombosis is associated with hyperglycaemia at diagnosis: a case-control study

J Hermanides, DM Cohn, JH DeVries, TPW Kamphuisen, R Huijgen, JCM Meijers, JBL Hoekstra and HR Büller

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ABSTRACT

**Background** Patients with (undiagnosed) diabetes mellitus, impaired glucose tolerance or stress-induced hyperglycaemia may be at greater risk for venous thrombosis and present with relative hyperglycaemia during the thrombotic event.

**Objectives** To assess whether venous thrombosis is associated with hyperglycaemia at diagnosis.

**Patients/methods** We performed a case-control study, derived from a cohort of consecutive patients referred for suspected deep vein thrombosis. Cases were patients with confirmed symptomatic venous thrombosis of the lower extremity. Controls were randomly selected in a 1:2 ratio from individuals in whom this diagnosis was excluded. We measured plasma glucose levels upon presentation to the hospital.

**Results** In total, 188 patients with thrombosis and 370 controls were studied. The glucose cut-off level for the first to fourth quartiles were as follows: first quartile <5.3 mmol/l; second quartile 5.3 to 5.7 mmol/l; third quartile 5.7 to 6.6 mmol/l; and the fourth quartile >=6.6 mmol/l. When adjusted for body mass index, a known history of diabetes mellitus, age, sex, ethnicity and whether known risk factors for deep vein thrombosis were present, the odds ratios for deep vein thrombosis in the second, third and fourth quartiles of glucose levels compared with the first quartile were 1.59 (95% confidence interval [CI] 0.89 to 2.85), 2.04 (95% CI 1.15 to 3.62) and 2.21 (95% CI 1.20 to 4.05), respectively, p for trend =0.001.

**Conclusions** Increased glucose levels measured at presentation were associated with venous thrombosis. Experimental evidence supports a potential causal role for hyperglycaemia in this process. As this is the first report on the association between (stress) hyperglycaemia and venous thrombosis, confirmation in other studies is required.
INTRODUCTION

Venous thromboembolism (VTE) is a common disease with an annual incidence of 2-3 per 1000 inhabitants. Both acquired and inherited risk factors are known to play a role in the development of thrombosis. Nevertheless, in approximately 25% of patients with VTE neither an acquired nor an inherited risk factor can be demonstrated. Evidence is growing that classic risk factors for arterial disease are also involved in the development of VTE. Hyperglycaemia is associated with arterial thrombosis and, indeed, patients with diabetes mellitus or the metabolic syndrome also have an increased risk of VTE. This increased risk of VTE can in part be explained by the platelet activation and hypercoagulability present in diabetes mellitus. Activation of the coagulation system has also been observed in acute experimentally induced hyperglycaemia in healthy male volunteers. During acute illness such as myocardial infarction, a phenomenon called stress hyperglycaemia may occur independently of the presence of known diabetes. As hyperglycaemia stimulates coagulation, we hypothesised that higher glucose levels -independent of known diabetes mellitus- would be more common in patients presenting with acute VTE.

METHODS

A case-control study was performed. Cases and controls were selected from the Amsterdam Case-Control Study on Thrombosis, which was initiated in 1999 to identify new risk factors for deep vein thrombosis (DVT). All consecutive outpatients older than 18 years referred to the Academic Medical Centre in Amsterdam between September 1999 and August 2006 with clinically suspected DVT of the lower extremity were eligible for this study. The study protocol was approved by the Medical Ethics Review Committee and all participants provided written informed consent. At presentation, the patient’s medical history was obtained through a standardised questionnaire including specific questions about symptom duration, presence of known risk factors (concomitant malignancy, pregnancy, use of hormonal replacement therapy, oral contraceptives or selective oestrogen receptor modulators, recent trauma (within last 60 days), being bedridden for >3 days, uncommon travel (>6hrs) within the last 3 months, paralysis of the symptomatic leg, or surgery within the last 4 weeks), concomitant diseases and medication use. In addition, body mass index (BMI) was calculated. Cases were patients with thrombosis of the lower extremity confirmed by compression
ultrasonography, including proximal DVT (i.e. proximal thrombosis of the iliac or superficial femoral vein, calf vein thrombosis, involving at least the upper third part of the deep calf veins), symptomatic calf vein thrombosis, and superficial thrombophlebitis. The diagnosis was confirmed following a diagnostic management strategy, based on the Wells’ criteria\textsuperscript{15} and a Tinaquant D-dimer assay (Roche Diagnostics, Basel, Switzerland), followed by compression ultrasound if indicated as validated and described previously.\textsuperscript{16} Controls were selected in a 1:2 ratio from those individuals in whom thrombosis was ruled out using the above mentioned strategy. Selection was performed randomly, only taking into account the male/female ratio of the cases.

**Sample storage and laboratory analysis**

On admission and prior to diagnostic testing, blood samples were drawn and collected in tubes containing 0.109 mmol/l trisodium citrate. Within one hour after collection, platelet poor plasma was obtained by centrifugation twice for 20 min at 1600 x g and 4 C. The plasma was stored in 2 ml cryovials containing 0.5 ml of plasma at -80 C.

Glucose was measured using the HK/G-6PD method (Roche/Hitachi, Basel, Switzerland) and corrected for the 10% dilution with sodium citrate. To assess whether elevated glucose levels were related to an acute phase response induced by the thrombotic event itself, we analysed C-reactive protein (CRP) levels from 20 cases and 20 controls, randomly selected from each quartile, giving a total of 160 patients.

**Statistical analysis**

Results are presented as mean ± standard deviation or median with interquartile range (IQR), depending on the observed distribution. The primary objective of this study was to assess the relationship between glucose levels at presentation and VTE, which was expressed as odds ratios (ORs), with 95% confidence intervals. Glucose levels of the controls were divided into quartiles, as glucose levels are typically non-normally distributed. Subsequently, the cases were assigned to these quartiles according to their admission glucose values. Binary logistic regression was used. The regression model was created on the basis of clinically relevant potential confounders (BMI, concomitant known diabetes mellitus, sex, ethnicity, age at diagnosis, and whether known risk factors for VTE were present). Furthermore, ORs were calculated for cases in which the diagnosis of thrombosis was restricted to DVT only, excluding calf vein thrombosis and superficial
Venous thrombosis is associated with hyperglycaemia at diagnosis

thrombophlebitis. To assess the correlation between glucose levels and CRP levels a scatter plot was performed and the correlation (expressed in r) coefficient was calculated. All statistical analyses were performed in SPSS version 15.0 (SPSS Inc., Chigaco, IL, USA).

RESULTS

In total 188 patients with confirmed thrombosis and 370 controls were included in this study, as blood samples were not available for two cases and 10 controls. The baseline characteristics of the two study groups are shown in Table 1. Mean age and gender distribution were comparable. The control group consisted of a smaller proportion of white patients and a greater proportion of black patients as compared with the cases. The mean BMI was higher in the control group, as tended to be the number of patients with known diabetes mellitus. Median glucose levels were 5.9 mmol/l (IQR 5.3 to 6.6) in patients with thrombosis, and 5.6 mmol/l (IQR 5.2 to 6.6) in the controls. In thrombosis patients, 38% had one or more acquired risk factors and the distribution of thrombosis was as follows: 82% had DVT, 6% had calf vein thrombosis, and the remaining 12% had superficial thrombophlebitis. The cut-off glucose levels were as follows: first quartile <5.3 mmol/l (n=141); second quartile 5.3 to 5.7 mmol/l (n=134); third quartile 5.7 to 6.6 mmol/l (n=139); and fourth quartile >=6.6 mmol/l (n=144) (Table 2).

After adjustment for BMI, concomitant known diabetes mellitus, sex, ethnicity, age at diagnosis, and whether known risk factors for VTE were present, the ORs for thrombosis in the second, third and fourth quartiles of glucose levels as compared with the first quartile were 1.40 (95% CI 0.82 to 2.85), 1.69 (95 % CI 1.00 to 2.87) and 1.94 (95% CI 1.12 to 3.39), respectively; p for trend =0.01. The same trend of an increasing OR could be observed when adjusting only for BMI, age, sex and known diabetes mellitus. As most risk factors predominantly relate to DVT a separate analysis was planned for DVT only, thus excluding patients with superficial thrombophlebitis or calf vein thrombosis, leaving 154 cases and 370 controls. Here also, the OR increases with glucose levels: 1.59 (95% CI 0.89 to 2.85), 2.04 (95% CI 1.15 to 3.62) and 2.21 (95% CI 1.20 to 4.05) for the second, third and fourth quartile of glucose levels, respectively (see Table 2, p for trend =0.001). Finally, the Spearman rank correlation coefficient for CRP and plasma glucose was 0.09, with a p-value of 0.27.
Table 1 - baseline characteristics of the two study groups

<table>
<thead>
<tr>
<th></th>
<th>Cases (n=188)</th>
<th>Controls (n=370)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years (mean ±SD)</td>
<td>57±17</td>
<td>56±16</td>
</tr>
<tr>
<td>Female (%)</td>
<td>57.4</td>
<td>58.1</td>
</tr>
<tr>
<td>Ethnicity (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>- White</td>
<td>78.7</td>
<td>69.2</td>
</tr>
<tr>
<td>- Black</td>
<td>10.1</td>
<td>18.1</td>
</tr>
<tr>
<td>- Asian/Pacific islander</td>
<td>2.7</td>
<td>4.2</td>
</tr>
<tr>
<td>- Other</td>
<td>8.5</td>
<td>8.5</td>
</tr>
<tr>
<td>BMI kg/m² (median, IQR)</td>
<td>26.6 (23.9 to 29.1)</td>
<td>27.2 (24.2 to 31.3)</td>
</tr>
<tr>
<td>Diabetes type 1 or 2 (%)</td>
<td>3.7</td>
<td>10.0</td>
</tr>
<tr>
<td>Glucose mmol/l (median, IQR)</td>
<td>5.9 (5.3 to 6.6)</td>
<td>5.6 (5.2 to 6.6)</td>
</tr>
</tbody>
</table>

Known risk factors: concomitant malignancy, pregnancy, use of hormonal replacement therapy, oral contraceptives or selective estrogen receptor modulators, recent trauma (within last 60 days), bedridden > 3 days, uncommon travel (> 6hrs) within the last 3 months, paralysis of the symptomatic leg, or surgery within the last 4 weeks.

Table 2 - odds ratios (ORs) for venous thromboembolism.

<table>
<thead>
<tr>
<th>Quartile (glucose mmol/l)</th>
<th>Cases</th>
<th>Controls</th>
<th>Crude OR (95% CI)</th>
<th>Adjusted OR* (95% CI)</th>
<th>Cases†</th>
<th>Controls†</th>
<th>Crude OR† (95% CI)</th>
<th>Adjusted OR†† (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st: &lt; 5.3</td>
<td>39</td>
<td>102</td>
<td>reference</td>
<td>reference</td>
<td>28</td>
<td>102</td>
<td>reference</td>
<td>reference</td>
</tr>
<tr>
<td>2nd: 5.3 to 5.7</td>
<td>46</td>
<td>88</td>
<td>1.37 (0.82 to 2.28)</td>
<td>1.40 (0.82 to 2.38)</td>
<td>37</td>
<td>88</td>
<td>1.53 (0.87 to 2.70)</td>
<td>1.59 (0.89 to 2.85)</td>
</tr>
<tr>
<td>3rd: 5.7 to 6.6</td>
<td>52</td>
<td>87</td>
<td>1.56 (0.94 to 2.59)</td>
<td>1.69 (1.00 to 2.87)</td>
<td>46</td>
<td>87</td>
<td>1.93 (1.11 to 3.34)</td>
<td>2.04 (1.15 to 3.62)</td>
</tr>
<tr>
<td>4th: ≥ 6.6</td>
<td>51</td>
<td>93</td>
<td>1.43 (0.87 to 2.37)</td>
<td>1.94 (1.12 to 3.39)</td>
<td>43</td>
<td>93</td>
<td>1.68 (0.97 to 2.93)</td>
<td>2.21 (1.20 to 4.05)</td>
</tr>
</tbody>
</table>

p for trend = 0.14 p for trend = 0.01 p for trend = 0.05 p for trend = 0.001

* adjusted for BMI, known diabetes mellitus, sex, age, ethnicity and known risk factors
†analyses for deep venous thrombosis only
††analyses for deep venous thrombosis only, adjusted for BMI, diabetes mellitus, sex, age, ethnicity and known risk factors
CI=confidence interval
DISCUSSION

In this case-control study, increased glucose levels measured at the time of presentation were associated with venous thrombosis. This could be a relevant clinical concept as the general population is becoming increasingly glucose intolerant. The relationship between glucose and DVT was not readily explained by an acute phase reaction due to the thrombotic event itself.

Whereas our results indicate that increased glucose levels and VTE coincide, it is impossible with the current design to demonstrate a causal relationship. However, a causal relationship seems plausible. To assess this one can apply the diagnostic criteria for causation. A causal relationship is supported by the available biological evidence from experiments in humans. Stegenga et al. showed that experimentally induced acute hyperglycaemia activates the coagulation system in healthy volunteers. From a pathophysiologic point of view, hyperglycaemia is known to induce coagulation activation through glycocalyx damage, up regulation of tissue factor, non-enzymatic glycation and the development of increased oxidative stress. Long term exposure to hyperglycaemia such as occurs in diabetes mellitus, is a known risk factor for VTE. In addition, the effect of hyperglycaemia on coagulation seems to be modifiable in diabetes patients, as treating hyperglycaemia among these patients led to down regulation of coagulation activation in several randomised controlled trials. Furthermore, our results are in line with the findings by Mraovic et al. who demonstrated that hyperglycaemia increases the risk of pulmonary embolism after major orthopaedic surgery. Thus, direct and indirect evidence supports a possible association for acute and chronic hyperglycaemia in the development of VTE. Furthermore, the association is consistent from this study to other studies, which is in line with the criterion for repetitive demonstration of causality.

In this study, an adjusted OR of 2.21 (95 % CI 1.20 to 4.05) for DVT was observed in the highest quartile which suggests a strong relationship. In comparison, the OR for the well established risk factor for VTE, the prothrombin 20210A mutation is 2.8 (95% CI 1.4 to 5.6). The OR for venous thrombosis increases with increasing glucose levels, from 1.40 (95% CI 0.82 to 2.38) in the second quartile to 1.69 (95% 1.00 to 2.87) in the third quartile and 1.94 (95 % CI 1.12 to 3.39) in the fourth quartile. We tested for differences in ORs among the quartiles of glucose levels and found a significant linear trend ($p=0.01$). This is in concordance with a dose-response gradient, another criterion for causality.
The question arises of whether elevated glucose levels during a VTE result from the inflammatory and counter regulatory hormone action initiated by the VTE event itself, or whether hyperglycaemia preceded the VTE event. Although a significant proportion of the patients with hyperglycaemia during an episode of VTE will have an undisturbed glucose tolerance at follow-up, undiagnosed impaired glucose tolerance is likely to have been present in a proportion of patients before the VTE event itself, and may therefore have contributed to the development of thrombosis. We therefore suspect a temporal relationship. In addition, no correlation was found between the acute phase reaction, measured by CRP, and glucose levels. The presence of stress hyperglycaemia during a thrombotic event, independent of its cause, could be relevant: it has been shown to have evident clinical consequences in patients with myocardial infarction and patients admitted to the intensive care unit (especially without known diabetes mellitus), although results from recent intervention trials have been disappointing.

Interestingly, we found a greater proportion of patients with diabetes in the control group than in the case group. In fact, this higher rate can be caused by referral bias. Patients with diabetes are usually under chronic medical care and are prone to leg- and foot problems that can resemble DVT, such as erysipelas. Thus, they are more easily referred for suspicion of DVT. We had no information on the use of anti-diabetic drugs. Differences in the distribution of diabetes treatment in both cases and controls could be a source of bias. However, we believe this effect to be limited. The model was adjusted for diabetes mellitus as a potential confounder.

Our study has several limitations. First, the control group consisted of patients with complaints of their legs instead of healthy controls. Consequently, it may be possible that glucose levels were increased in the controls because of an underlying disease such as infection. However, this would have led to an underestimation of the association between glucose and DVT. Second, the glucose levels were measured on admission, and it was unknown whether these were fasting or non-fasting samples. However, owing to the study design there were no differences between cases and controls with respect to the time of presentation and larger dispersion of glucose levels would therefore have affected cases as much as controls. Third, citrated plasma is not the plasma of choice for determining glucose and CRP levels, because of the dilution with sodium citrate. Also, sodium citrate does not inhibit ex vivo glycolysis. However, we corrected glucose levels for the dilution and the obtained blood samples were centrifuged and stored within one hour thereby minimizing glycolysis. Again, as blood samples of both cases and controls were obtained and processed in the same manner, the results for glucose levels were
affected equally. Because this is the first report on the association between stress hyperglycaemia and VTE, confirmation in other studies is required.

In conclusion, our findings suggest that higher glucose levels are a risk factor for the development of venous thrombosis. It will therefore be of importance to analyse whether disturbed glucose homeostasis persists after the acute phase of venous thrombosis.

ACKNOWLEDGEMENTS

We would like to acknowledge M.M. Levi for assessing the manuscript and for his significant intellectual contribution. In addition we would like to acknowledge the “vasculists”, a group of medical students responsible for execution of this study, ranging from design of the study to recruitment and data collection.
REFERENCES


Venous thrombosis is associated with hyperglycaemia at diagnosis


Hip surgery sequentially induces stress hyperglycaemia and activates coagulation

J Hermanides, R Huijgen, CP Henny, N Haj Mohammad, JBL Hoekstra, MM Levi and JH DeVries

The Netherlands Journal of Medicine, 2009 June;67(6):226-9
ABSTRACT

**Background** A frequent complication of orthopaedic procedures is venous thromboembolism (VTE). Hyperglycaemia has been shown to activate the coagulation system and is associated with postoperative morbidity and mortality. Therefore we hypothesised that glucose levels increase during orthopaedic surgery and are associated with an activation of the coagulation system.

**Methods** Nine adult patients undergoing elective hip replacement were included. Venous blood samples were taken before, during and after surgery. Plasma glucose levels, factor VIII clotting activity (fVIII:c), von Willebrand ristocetin cofactor activity, von Willebrand factor antigen and prothrombin fragment 1+2 were measured.

**Results** Immediately after induction of anaesthesia, plasma glucose levels started to increase until the second day postoperatively (peak 8.0 mmol/l). After seven weeks glucose values had returned to baseline (6.1 mmol/l), \( p < 0.001 \) with ANOVA. All coagulation parameters increased during surgery, subsequent to the rise in glucose. The change in mean FVIII:c and von Willebrand ristocetin cofactor activity significantly correlated with mean glucose values.

**Conclusions** These observations indicate that total hip replacement surgery causes an increase in glucose levels that precedes the proportional rise of the measured coagulation parameters. This suggests a possible role of glucose in the activation of the coagulation system during hip surgery.
INTRODUCTION

A frequent complication of surgical procedures is venous thromboembolism (VTE), manifesting as deep venous thrombosis or pulmonary embolism.\(^1\) Especially after orthopaedic surgery the incidence of postoperative symptomatic VTE is high, occurring in 1.5 to 10% of the patients despite adequate anticoagulant prophylaxis.\(^2\) Risk factors for the development of VTE after surgery include underlying malignancy and advanced age.\(^2\) In an experimental setting hyperglycaemia has been shown to activate the coagulation system in healthy volunteers, in particular by stimulating the tissue factor pathway.\(^3;4\) This is of interest since hyperglycaemia in response to surgery is a common finding.\(^5-7\) Counter regulatory hormone action initiated by the surgical trauma can induce “stress hyperglycaemia”, even without known diabetes mellitus.\(^8\) Recently, pre-operative hyperglycaemia has been identified as a risk factor for pulmonary embolism, independent of diabetes mellitus.\(^9\) Thus, we hypothesised that glucose levels increase during orthopaedic surgery and may contribute and therefore be related to an activation of the coagulation system.

MATERIALS AND METHODS

Study design and population
We performed an observational study, assessing the correlation between perioperative changes in plasma glucose levels and a number of coagulation parameters. Adult patients undergoing elective hip replacement surgery were recruited from the Department of Orthopaedic Surgery at the Academic Medical Centre, University of Amsterdam, the Netherlands. Exclusion criteria were: previous VTE, revision hip replacement, use of \(\beta\)-blockers, known diabetes mellitus, inability or unwillingness to give written informed consent, and inability to be followed up. The study was approved by the Medical Ethics Commission of the Academic Medical Centre, University of Amsterdam and written informed consent was obtained from each patient.

Data collection
Clinical data including date of birth, sex, height, weight, blood and indication for hip replacement were recorded. Venous blood samples were taken at 14 set points in time (Figure 1). The samples on the day of surgery were taken in the fasting
state. The samples on the other days (non-fasting) were taken between 8 and 10 am to exclude the influence of circadian fluctuations on the haemostatic parameters.

**Laboratory determinations**

Blood was collected in ice-cooled tubes of 2.7 ml containing 0.109 M trisodium citrate, which were centrifuged within one hour. The citrate samples were centrifuged at 3000 rpm at 4 °C for 20 minutes and the separated plasma again at 4000 rpm and 4 °C for five minutes and stored immediately at -80 °C. Plasma glucose was measured using the HK/G-6PD method (Roche/Hitachi, Basel, Switzerland) and corrected for the 10% dilution with sodium citrate. Factor VIII clotting activity (FVIII:c) and von Willebrand ristocetin cofactor activity (vWF:RiCof) assays were performed on an automated coagulation analyser (Behring Coagulation System) with reagents and protocols from the manufacturer (Dade Behring, Marburg, Germany), and are expressed as a percentage of reference activity. Measurements of prothrombin fragment 1+2 (F1+2) (Dade Behring, Marburg, Germany) and von Willebrand factor antigen (vWF:Ag) (antibodies from Dako, Glostrup, Denmark) were performed by ELISA.

**Statistical analyses**

Mean glucose levels perioperatively and during surgery were plotted against time. Sequential glucose values were analysed with the repeated measurements ANOVA. For the ANOVA analyses, missing values per patient were linearly interpolated. Post-hoc testing was performed using the paired t-test with Holm’s sequential Bonferroni correction, comparing the non-fasting samples with the baseline mean glucose values and the fasting samples with the pre-induction sample. To assess the correlation between mean glucose levels and mean FVIII:c, vWF:Ag, vWB:RiCof., F1+2 values we calculated the correlation coefficient. Correlation was considered relevant in case of r >0.5. The level of significance was p<0.05.

**RESULTS**

During the study period 17 patients scheduled for elective hip replacement surgery were evaluated. Nine patients met the inclusion criteria and provided written informed consent. The investigated cohort included five males and four females with a mean age of 63 years (SD 22 years) and mean BMI of 27.7 kg/m² (SD 2.8). Indication for hip surgery was coxarthrosis in seven patients, one case of idiopathic femur head necrosis and prednisone induced femur head necrosis in one patient.
This last subject had stopped taking prednisone two years before inclusion in this study. Low-molecular weight heparin (LMWH), starting the day before surgery, was used as thromboprophylaxis in five patients. One patient started LMWH the day after surgery and three patients used oral anticoagulants.

**Glucose values**

Mean plasma glucose levels and the number of successful samples per time point are depicted in Figure 1 and Table 1. The repeated measurements ANOVA for all sequential glucose samples was $p<0.001$. Missing values are due to occlusion of the intravenous sampling catheter during surgery. Mean plasma glucose levels changed significantly during surgery as compared with pre-induction. Directly after induction of anaesthesia glucose levels increased from 5.6 to 6.0 mmol/l ($p=0.002$). Two hours after surgery, glucose levels were still significantly increased as compared with pre-induction (7.3 mmol/l, $p=0.01$). Postoperatively non-fasting glucose levels peaked at the second postoperative day and remained increased up to the 4th day after surgery as compared to baseline non-fasting mean glucose values. After seven weeks non-fasting glucose levels returned to baseline values.

**Coagulation factors**

The mean levels of FVIII:c, vWF:Ag, vWF:RiCof. and F1+2 are presented in Table 1. All values increased significantly during surgery. FVIII:c and F1+2 returned to baseline values seven weeks after surgery. However, vWF:Ag and vWF:RiCof remained elevated. In Figure 1 the increase in mean levels of coagulation factors per time point are shown. In contrast with the steep increase in glucose levels after placement of the prosthesis cup (S4), vWF:Ag, vWF:RiCof and FVIII:c levels somewhat lagged behind the glucose pattern. Both FVIII:c ($r=0.69, p=0.03$) and vWF:RiCof ($r=0.69, p=0.006$) were significantly correlated with the mean glucose levels. Correlation coefficients of F1+2 ($r=0.58, p=0.07$) and vWF:Ag ($r=0.59, p=0.06$) had borderline significance.
<table>
<thead>
<tr>
<th>Time</th>
<th>Glucose (mmol/l)</th>
<th>F1+2 (nmol/L)</th>
<th>vWF:Ag (IU/dL)</th>
<th>vWF:RiCof (IU/dL)</th>
<th>FVIII:c (IU/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surgery -1 day</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before induction</td>
<td>6.2 (±1.0)</td>
<td>1.0 (±0.3)</td>
<td>116.8 (±37.2)</td>
<td>101.8 (±34.3)</td>
<td></td>
</tr>
<tr>
<td>Infection</td>
<td>5.6 (±0.4)</td>
<td>1.1 (±0.5)</td>
<td>115.4 (±28.0)</td>
<td>105.4 (±36.7)</td>
<td></td>
</tr>
<tr>
<td>After skin incision</td>
<td>6.0 (±0.7)</td>
<td>1.0 (±0.5)</td>
<td>103.6 (±28.2)</td>
<td>101.0 (±35.2)</td>
<td></td>
</tr>
<tr>
<td>After placing cup</td>
<td>S4 6.0 (±0.7)</td>
<td>1.0 (±0.5)</td>
<td>102.1 (±28.2)</td>
<td>104.5 (±35.2)</td>
<td></td>
</tr>
<tr>
<td>After placing prosthetic</td>
<td>S5 6.9 (±0.8)</td>
<td>1.3 (±0.4)</td>
<td>122.0 (±46.2)</td>
<td>140.4 (±59.8)</td>
<td></td>
</tr>
<tr>
<td>2 hours after surgery</td>
<td>S6 7.3 (±1.4)</td>
<td>2.0 (±0.4)</td>
<td>123.6 (±50.0)</td>
<td>138.6 (±58.6)</td>
<td></td>
</tr>
<tr>
<td>Surgery +1 day</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Before induction</td>
<td>5.6 (±0.4)</td>
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<td></td>
<td></td>
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<td>Surgery +3 days</td>
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<td>5.6 (±0.4)</td>
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<tr>
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<td></td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Before induction</td>
<td>5.6 (±0.4)</td>
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<td>S6 7.3 (±1.4)</td>
<td>2.0 (±0.4)</td>
<td>123.6 (±50.0)</td>
<td>138.6 (±58.6)</td>
<td></td>
</tr>
<tr>
<td>Surgery +49 days</td>
<td>Final</td>
<td>6.1 (±0.8)</td>
<td>1.1 (±0.7)</td>
<td>164.6 (±57.9)</td>
<td>149.2 (±62.7)</td>
</tr>
</tbody>
</table>

Table 1 - Mean levels of glucose and coagulation parameters per time point, displayed with mean ± SD.
Figure 1 - Mean per- and postoperative glucose levels (2 upper graphs are identical) and coagulation parameters with 95% CI. +p < 0.05 as compared to baseline, *p < 0.05 as compared to S1 (glucose fasting samples only) Repeated measurements ANOVA: p < 0.001 for glucose, vWF:ag, vWF:RiCof, F1+2 and FVIII:c

**Sampling time points**

<table>
<thead>
<tr>
<th>Sampling point</th>
<th>Description</th>
<th>Sample Size</th>
<th>Time After Surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline (n=9)</td>
<td>Baseline: surgery -1 day</td>
<td></td>
<td></td>
</tr>
<tr>
<td>S1 (n=7)</td>
<td>Before induction</td>
<td>D1 (n=9)</td>
<td>Surgery +1 day</td>
</tr>
<tr>
<td>S2 (n=8)</td>
<td>After induction</td>
<td>D2 (n=7)</td>
<td>Surgery +2 days</td>
</tr>
<tr>
<td>S3 (n=8)</td>
<td>After skin incision</td>
<td>D3 (n=9)</td>
<td>Surgery +3 days</td>
</tr>
<tr>
<td>S4 (n=8)</td>
<td>After placing cup</td>
<td>D4 (n=7)</td>
<td>Surgery +4 days</td>
</tr>
<tr>
<td>S5 (n=8)</td>
<td>After placing prosthesis</td>
<td>Final (n=9)</td>
<td>Surgery +49 days</td>
</tr>
<tr>
<td>S6 (n=8)</td>
<td>2 hours after surgery</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
DISCUSSION

In this observational study we have demonstrated how plasma glucose levels increase in response to hip replacement surgery. Following this rise in glucose, FVIII:c, vWF:Ag, vWF:RiCof and F1+2 levels also increased. These changes in mean glucose levels and mean levels of coagulation parameters during hip replacement surgery were closely correlated. All measured parameters remained elevated for several days up to seven weeks postoperatively.

The link between glucose increase and activation of the coagulation system has been established before. Stegenga and co-workers showed in clamp studies that hyperglycaemia leads to up regulation of coagulation parameters in healthy volunteers, measured by soluble tissue factor and thrombin-antithrombin complexes. Furthermore, exposure to prolonged hyperglycaemia (diabetes mellitus) is an established risk factor for VTE. Coagulation activation by hyperglycaemia may be explained by mechanisms such as glycocalyx damage, non-enzymatic glycation, or the development of increased oxidative stress. From the present study we cannot conclude whether increasing glucose levels directly activates the coagulation system. Activation of coagulation could be due to other causes, such as vascular damage and bleeding induced by the surgery. However, it is of interest to note that the rise in glucose levels precedes the increase in the measured coagulation parameters and is closely correlated with these parameters.

Our study was limited by the small sample size (n=9). This was therefore a pilot study, to determine whether hip surgery does indeed cause hyperglycaemia and whether this is associated with activation of the coagulation system. To investigate the direct influence of perioperative glucose levels on coagulation parameters, a randomised controlled trial is needed, comparing an intervention group in which normoglycaemia is maintained with untreated controls, as in our study population.

A consideration in interpreting the results is the possible lowering of coagulation parameters in response to the use of thromboprophylaxis and anticoagulants, especially the use of oral anticoagulants in three patients and the influence on F1+2. However, one would have expected an even larger increase in the coagulation parameters when no anticoagulants or thromboprophylaxis were used, and this is therefore not likely to have biased the results.

Glucose values were measured both fasting (preoperatively) and non-fasting (perioperatively). In the analyses we have attempted to overcome this limitation by comparing the non-fasting samples to the baseline mean glucose values and the fasting samples with the pre-induction sample. It should also be noted that the
medium in which the blood was collected, trisodium citrate, is not the medium of choice for glucose measurements. We have however corrected for the dilution factor. In addition, samples were stored in ice-cooled tubes which were centrifuged immediately. This limits possible glycolysis.

In conclusion, our observations indicate that total hip replacement surgery causes glucose levels to increase, prior to a rise in the concentration of the measured coagulation parameters. This suggests a possible role of glucose in the activation of the coagulation system during hip surgery. Confirmation of this observation in interventional studies is needed.
REFERENCES


Stress-induced hyperglycaemia and venous thromboembolism following total hip or total knee arthroplasty

J Hermanides, DM Cohn, JH DeVries, PW Kamphuisen, S Kuhls, M Homering, JBL Hoekstra, AW Lensing and HR Büller

Submitted for publication
ABSTRACT

Background Stress-induced hyperglycaemia is common during orthopaedic surgery. In addition, hyperglycaemia activates coagulation. Whether stress-induced hyperglycaemia is associated with symptomatic or asymptomatic venous thromboembolism (VTE) following orthopaedic surgery is unknown.

Methods We performed post-hoc analyses in the four RECORD studies (REgulation of Coagulation in major Orthopedic surgery reducing the Risk of Deep venous thrombosis and pulmonary embolism). Separate analyses were performed for patients undergoing total hip or knee replacement. Outcome measures were symptomatic VTE and “total VTE” (defined as the composite of symptomatic VTE, asymptomatic DVT assessed by per protocol venography and all cause mortality). Glucose levels were measured at day 0 (pre-surgery visit) and post-surgery on day 1, categorised into quartiles, based on the distribution in the respective cohorts. The influence of glucose, adjusted for BMI, age, gender and diabetes mellitus on VTE was assessed by logistic regression analyses.

Results A total of 12383 patients were eligible for assessment of symptomatic VTE and 8512 patients were eligible for assessment of total VTE. Increased glucose levels after total hip replacement were associated with total VTE; adjusted OR highest versus lowest quartile 1.9 (95%CI 1.3 to 3.0). Furthermore, increase in glucose levels during hip surgery was associated with total VTE (OR highest versus lowest quartile 1.8 (95%CI 1.2 to 2.8). This was not observed in patients undergoing total knee replacement.

Conclusion Stress-induced hyperglycaemia following total hip replacement was associated with total VTE. This was not demonstrated in patients undergoing total knee replacement, which is likely due to the surgical procedure.
INTRODUCTION

Venous thromboembolism (VTE) may manifest as either deep venous thrombosis (DVT) or pulmonary embolism (PE), or a combination of both. VTE affects 2-3 persons per 1000 inhabitants annually in Western Societies. Acquired risk factors, inherited risk factors or both can be found in approximately 75% of patients with VTE. This implies, that in approximately 25% of patients with VTE no risk factors can be identified.

In several reports, acute hyperglycaemia was shown to cause coagulation activation in an experimental setting as demonstrated by increased levels of thrombin-antithrombin complexes and soluble tissue factor. During acute illness or surgery, a phenomenon called stress hyperglycaemia may occur independently of the presence of known diabetes. Indeed, hip surgery has been shown to induce hyperglycaemia peaking the days after the procedure, followed by post-operative procoagulant activity peaking on the third and fourth postoperative days. Hyperglycaemia at presentation has recently been shown to be associated with VTE in an outpatient population. Whether stress-hyperglycaemia is associated with VTE in hospitalised patients, such as orthopaedic patients, has not been previously addressed. The associated risk of hyperglycaemia could be of particular interest in surgical patients, since the coagulation system is already activated due to the surgical procedure. Furthermore, VTE is a frequently occurring complication following orthopaedic surgery. Despite anticoagulant prophylaxis, symptomatic VTE occurs in approximately 2% of all patients undergoing hip or knee replacements. In this study we aimed to assess whether pre- and postoperative hyperglycaemia is associated with (a)symptomatic VTE.

METHODS

Patients

For the present analysis we made use of the large phase III trial programme: “REgulation of Coagulation in major Orthopaedic surgery reducing the Risk of Deep venous thrombosis and pulmonary embolism studies” (RECORD 1-4). These trials compared the efficacy and safety of Rivaroxaban (a direct factor Xa inhibitor) 10 mg qd relative to standard treatment with Enoxaparin 40 mg qd or 30 mg b.i.d. Because efficacy and safety outcomes, as well as independent, blinded adjudication committees were the same in all RECORD studies, the studies allowed pooling of the data. Patients were eligible if they were aged 18 years or
older and were scheduled for elective total hip or total knee arthroplasty. Major exclusion criteria included active bleeding or high risk of bleeding, significant liver disease, anticoagulant therapy that could not be interrupted, use of HIV-protease-inhibitors and a contraindication for prophylaxis with enoxaparin or a condition that would require a dose adjustment for enoxaparin. Detailed in- and exclusion criteria were reported in the original publications of the RECORD studies.11-14

Procedures
Deep-vein thrombosis was assessed per protocol, by ascending, bilateral venography with a standardised technique.15 This was performed at day 36 (range 32 to 40) in patients with total hip replacements (RECORD 1 and 2)11;12 and at day 13 (range 11 to 15) in patients with total knee replacement (RECORD 3 and 4).13;14 Symptomatic VTE was objectively confirmed by standard imaging techniques. Treatment duration was 5 weeks for RECORD study 1 and 2 (including the 3 weeks of placebo treatment in the comparator group). Treatment duration in RECORD 3 and 4 was 2 weeks. Patients were followed up for 30 to 35 days after the last dose. Glucose levels were sampled upon admission (day 0) and 6 hours after surgery (day 1). All samples were analysed in the central laboratory.

Outcomes
The aim of this study was to assess whether hyperglycaemia (measured pre- and post-surgery) was associated with an increased risk of VTE. We assessed the effect of hyperglycaemia on symptomatic VTE (until Day 42 in hip replacement and Day 17 in knee replacement) in the participants included in the safety population of the four RECORD studies. The safety population was defined as patients who received at least one dose of study medication. Furthermore, we investigated the association between hyperglycaemia and total VTE, which was defined as the composite outcome of symptomatic VTE and asymptomatic DVT as detected by venography and all cause mortality. The analyses for total VTE were performed in the modified intention to treat (mITT) population, comprising all patients from the safety analyses with surgery and adequate assessment of both proximal and distal veins on venography. Only events occurring in the planned treatment phase of the studies were considered.

Statistical Analyses
Descriptive results are presented as mean ± standard deviation (SD) or median with interquartile range (IQR). To investigate the association of hyperglycaemia
and VTE multiple logistic regression analyses were performed separately for patients undergoing total hip and total knee arthroplasty. Separate analyses were carried out to assess the influence of glucose on Day 0 (pre-surgery) and Day 1 (post-surgery), and of the difference in glucose levels (Day 1-Day 0) on symptomatic VTE and total VTE. In all analyses glucose levels were categorised into quartiles, based on the distribution in the respective cohorts. Adjusted odds ratios (OR) for categorised glucose levels were derived from a logistic regression model with variables for glucose, treatment group, study and other relevant covariates (BMI (<25, 25 to 35, >=35), age (<65, 65 to 75, >75 years), gender, concomitant known diabetes mellitus). The reported p-value (from likelihood ratio test on 3 d.f.) for glucose refers to a global test of differences in outcome rates with categorised glucose levels. All statistical analyses were performed in SAS version 9.1 (SAS institute, Cary, NC).
RESULTS

Baseline characteristics
The safety population of the four RECORD studies consisted of 12383 patients, of whom 6890 underwent total hip arthroplasty and 5493 total knee arthroplasty, respectively. The baseline characteristics of both cohorts are shown in Table 1. High BMI and female gender were more common in the knee arthroplasty cohort (mean BMI 30 kg/m² vs. 28 kg/m², and 66% vs. 55%, respectively). Mean age was slightly higher in the knee surgery cohort: 66 years vs. 63 years. The mITT population comprised 8512 patients (hip replacement 4886 patients, knee replacement 3626 patients).

<table>
<thead>
<tr>
<th></th>
<th>Total hip arthroplasty (RECORD 1&amp;2) (n=6890)</th>
<th>Total knee arthroplasty (RECORD 3&amp;4) (n=5493)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age – years (mean ± SD)</td>
<td>63 (12)</td>
<td>66 (10)</td>
</tr>
<tr>
<td>Sex, female n (%)</td>
<td>3780 (55%)</td>
<td>3652 (66%)</td>
</tr>
<tr>
<td>Body-mass index – kg/m² (mean ± SD)</td>
<td>28 (5)</td>
<td>30 (6)</td>
</tr>
<tr>
<td>History of VTE, n (%)</td>
<td>132 (2%)</td>
<td>156 (3%)</td>
</tr>
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<td>Previous orthopaedic surgery, n (%)</td>
<td>1447 (21%)</td>
<td>1690 (31%)</td>
</tr>
<tr>
<td>Type of surgery, n (%)</td>
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<td></td>
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<tr>
<td>- Primary</td>
<td>6562 (95%)</td>
<td>5329 (97%)</td>
</tr>
<tr>
<td>- Revision</td>
<td>254 (4%)</td>
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</tr>
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<td>74 (1%)</td>
<td>45 (1%)</td>
</tr>
<tr>
<td>Type of anesthesia</td>
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<tr>
<td>- General only</td>
<td>1983 (29%)</td>
<td>1034 (19%)</td>
</tr>
<tr>
<td>- General and regional</td>
<td>619 (9%)</td>
<td>1126 (21%)</td>
</tr>
<tr>
<td>- Regional only</td>
<td>4215 (61%)</td>
<td>3292 (60%)</td>
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<tr>
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<tr>
<td>- None</td>
<td>0 (0%)</td>
<td>41 (1%)</td>
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<tr>
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<td>99 (40)</td>
</tr>
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<td>Time to mobilisation – days (mean ± SD)</td>
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<td>Ethnic origin, n (%)</td>
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<td>- White</td>
<td>5687 (83%)</td>
<td>4037 (73%)</td>
</tr>
<tr>
<td>- Asian</td>
<td>498 (7%)</td>
<td>736 (13%)</td>
</tr>
<tr>
<td>- Hispanic</td>
<td>329 (5%)</td>
<td>353 (6%)</td>
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<tr>
<td>- Black</td>
<td>103 (1%)</td>
<td>181 (3%)</td>
</tr>
<tr>
<td>- Other/missing</td>
<td>273 (4%)</td>
<td>186 (3%)</td>
</tr>
<tr>
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<tr>
<td>- Rivaroxaban</td>
<td>3437 (50%)</td>
<td>2746 (50%)</td>
</tr>
<tr>
<td>- Comparator (enoxaparin)</td>
<td>3453 (50%)</td>
<td>2747 (50%)</td>
</tr>
<tr>
<td>On glucose lowering therapy, n (%)</td>
<td>407 (6%)</td>
<td>654 (12%)</td>
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<tr>
<td>Diabetes Mellitus n (%)</td>
<td>532 (8%)</td>
<td>890 (16%)</td>
</tr>
<tr>
<td>Glucose measured on Day 0, n (%)</td>
<td>6844 (99%)</td>
<td>5433 (99%)</td>
</tr>
<tr>
<td>Glucose measured on Day 1, n (%)</td>
<td>6680 (97%)</td>
<td>5323 (97%)</td>
</tr>
<tr>
<td>Glucose measured on Day 0 &amp; Day 1, n (%)</td>
<td>6648 (96%)</td>
<td>5272 (96%)</td>
</tr>
</tbody>
</table>

Table 1-baseline characteristics of both cohorts (safety population)
VTE=venous thromboembolism, SD=standard deviation
Stress-induced hyperglycaemia & VTE following total hip or knee arthroplasty

**Total hip arthroplasty**
The median pre-operative glucose level at day 0 was 5.4 mmol/l (IQR 4.9 to 6.3, Table 2a). Glucose levels on Day 0 were not associated with either symptomatic VTE or total VTE ($p=0.22$ and $p=0.31$ respectively, see Table 2a).

At day 1 (post surgery), the median glucose level was 6.5 mmol/l (IQR 5.5 to 7.9, Table 2b). Glucose levels in the highest quartile (>7.9 mmol/l) were associated with both symptomatic VTE and total VTE, when compared to the lowest glucose quartile (<5.5 mmol/l): adjusted OR were 2.3 (95% CI 0.9 to 6.0) and OR 1.9 (95% CI 1.3 to 3.0), respectively. The $p$-value of the Likelihood Ratio test for glucose on Day 1 was significant for both outcomes ($p=0.04$ for symptomatic VTE and $p<0.0001$ for total VTE). In addition, the amount of increase of the glucose level between day 1 and day 0 was associated with total VTE ($p=0.01$, see Table 2c). Median difference of glucose levels between these two time points was 0.9 mmol/l (IQR -0.3 to 2.2). The highest quartile of this difference was associated with a nearly twofold increased risk for total VTE compared to the lowest quartile (adjusted OR 1.8, 95% CI 1.2 to 2.8). For symptomatic VTE no association with the difference of glucose on day 1 and day 0 could be observed ($p=0.24$, Table 2c).

**Total knee arthroplasty**
The distribution in glucose levels at day 0 and day 1 in patients undergoing knee arthroplasty was comparable to that in the hip surgery cohort. Median glucose was 5.5 mmol/l (IQR 4.9 to 6.4) at day 0 and 6.8 mmol/l (IQR 5.7 to 8.3) at day 1 (Table 3a and 3b).

For glucose levels measured at day 0, there was no association between glucose levels and symptomatic VTE ($p=0.46$, Table 3a). A non-significant trend was observed for total VTE at day 0 (Likelihood Ratio test: $p=0.14$). The adjusted OR for highest versus lowest quartile was 1.4 (95% CI 1.03 to 2.0, Table 3a). Glucose levels measured at day 1 were not significantly associated with symptomatic VTE: adjusted OR 1.8 (95% CI 0.8 to 4.1, Table 3b). For total VTE, the adjusted OR for highest versus lowest glucose quartile was 1.3 (95% CI 0.96 to 1.8, Table 3b).

No association was found between the increase in glucose levels (median difference 1.1 mmol/l, IQR -0.2 to 2.6) and VTE; adjusted OR for symptomatic VTE: 0.8 (95% CI 0.3 to 1.8) and for total VTE: 1.1 (95% CI 0.8 to 1.4, Table 3c).
Table 2- odds ratio for glucose levels measured at day 0, day 1 and difference in glucose levels between day 1 and day 0 in relation to symptomatic VTE and total VTE in hip surgery patients (RECORD 1&2)

a) quartiles glucose levels measured at day 0*

<table>
<thead>
<tr>
<th>All patients (N)</th>
<th>&lt;4.9</th>
<th>≥4.9 to 5.4</th>
<th>&gt;5.4 to 6.3</th>
<th>&gt;6.3</th>
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<tr>
<td>1487</td>
<td>1713</td>
<td>2014</td>
<td>1630</td>
<td></td>
</tr>
<tr>
<td>Symptomatic VTE (n)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>13</td>
<td>11</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>Crude OR (95%CI)</td>
<td>1 (ref)</td>
<td>2.3 (0.8 to 6.4)</td>
<td>1.6 (0.6 to 4.7)</td>
<td>1.1 (0.3 to 3.6)</td>
</tr>
<tr>
<td>Adjusted OR (95%CI)</td>
<td>1 (ref)</td>
<td>2.3 (0.8 to 6.5)</td>
<td>1.7 (0.6 to 4.9)</td>
<td>0.9 (0.3 to 3.2)</td>
</tr>
<tr>
<td>LR test</td>
<td>p=0.22</td>
<td></td>
<td></td>
<td></td>
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</tbody>
</table>

b) quartiles glucose levels measured at day 1*

<table>
<thead>
<tr>
<th>All patients (N)</th>
<th>&lt;5.5</th>
<th>≥5.5 to 6.5</th>
<th>&gt;6.5 to 7.8</th>
<th>&gt;7.8</th>
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</thead>
<tbody>
<tr>
<td>1590</td>
<td>1722</td>
<td>1671</td>
<td>1697</td>
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<tr>
<td>Symptomatic VTE (n)</td>
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<tr>
<td>6</td>
<td>4</td>
<td>6</td>
<td>17</td>
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<tr>
<td>Crude OR (95%CI)</td>
<td>1 (ref)</td>
<td>0.6 (0.2 to 2.2)</td>
<td>1.0 (0.3 to 3.0)</td>
<td>2.7 (1.1 to 6.8)</td>
</tr>
<tr>
<td>Adjusted OR (95%CI)</td>
<td>1 (ref)</td>
<td>0.6 (0.2 to 2.2)</td>
<td>0.9 (0.3 to 2.8)</td>
<td>2.3 (0.9 to 6.0)</td>
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<tr>
<td>LR test</td>
<td>p=0.04</td>
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c) quartiles difference in glucose levels day 1 - day 0*

<table>
<thead>
<tr>
<th>All patients (N)</th>
<th>≤-0.3</th>
<th>&gt;-0.3 to 0.9</th>
<th>&gt;0.9 to 2.2</th>
<th>&gt;2.2</th>
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</thead>
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<td>1633</td>
<td>1655</td>
<td>1699</td>
<td>1661</td>
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<tr>
<td>Symptomatic VTE (n)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>5</td>
<td>6</td>
<td>8</td>
<td>14</td>
<td></td>
</tr>
<tr>
<td>Crude OR (95%CI)</td>
<td>1 (ref)</td>
<td>1.2 (0.4 to 3.9)</td>
<td>1.5 (0.5 to 4.7)</td>
<td>2.8 (1.0 to 7.7)</td>
</tr>
<tr>
<td>Adjusted OR (95%CI)</td>
<td>1 (ref)</td>
<td>1.3 (0.4 to 4.3)</td>
<td>1.6 (0.5 to 4.8)</td>
<td>2.6 (0.9 to 7.3)</td>
</tr>
<tr>
<td>LR test</td>
<td>p=0.24</td>
<td></td>
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<td></td>
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</tbody>
</table>

VTE=venous thromboembolism; OR=Odds Ratio, LR test=Likelihood Ratio test for testing whether increase in glucose levels (in quartiles) has a significant influence on the occurrence of VTE. Total VTE is the composite of symptomatic VTE, asymptomatic DVT and all cause mortality.

*mmol/l
# Stress-induced hyperglycaemia & VTE following total hip or knee arthroplasty

<table>
<thead>
<tr>
<th>Table 3-</th>
<th>odds ratio for glucose levels measured at day 0, day 1 and difference in glucose levels between day 1 and day 0 in relation to symptomatic VTE and total VTE in knee surgery patients (RECORD 3&amp;4)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>a) quartiles glucose levels measured at day 0</strong>*</td>
<td></td>
</tr>
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<td><strong>all patients (N)</strong></td>
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<tr>
<td><strong>symptomatic VTE (n)</strong></td>
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<tr>
<td><strong>crude OR (95%CI)</strong></td>
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<tr>
<td><strong>adjusted OR (95%CI)</strong></td>
<td>1 (ref)</td>
</tr>
<tr>
<td><strong>LR test</strong></td>
<td></td>
</tr>
<tr>
<td><strong>patients valid for the modified intention to treat analyses (N)</strong></td>
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</tr>
<tr>
<td><strong>total VTE (n)</strong></td>
<td>72</td>
</tr>
<tr>
<td><strong>crude OR (95%CI)</strong></td>
<td>1 (ref)</td>
</tr>
<tr>
<td><strong>adjusted OR (95%CI)</strong></td>
<td>1 (ref)</td>
</tr>
<tr>
<td><strong>LR test</strong></td>
<td></td>
</tr>
<tr>
<td><strong>b) quartiles glucose levels measured at day 1</strong>*</td>
<td></td>
</tr>
<tr>
<td><strong>all patients (N)</strong></td>
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<tr>
<td><strong>symptomatic VTE (n)</strong></td>
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<tr>
<td><strong>crude OR (95%CI)</strong></td>
<td>1 (ref)</td>
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<tr>
<td><strong>adjusted OR (95%CI)</strong></td>
<td>1 (ref)</td>
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<tr>
<td><strong>total VTE (n)</strong></td>
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<tr>
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<td><strong>adjusted OR (95%CI)</strong></td>
<td>1 (ref)</td>
</tr>
<tr>
<td><strong>LR test</strong></td>
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</tr>
<tr>
<td><strong>c) quartiles difference in glucose levels day 1 - day 0</strong>*</td>
<td></td>
</tr>
<tr>
<td><strong>all patients (N)</strong></td>
<td>1331</td>
</tr>
<tr>
<td><strong>symptomatic VTE (n)</strong></td>
<td>13</td>
</tr>
<tr>
<td><strong>crude OR (95%CI)</strong></td>
<td>1 (ref)</td>
</tr>
<tr>
<td><strong>adjusted OR (95%CI)</strong></td>
<td>1 (ref)</td>
</tr>
<tr>
<td><strong>LR test</strong></td>
<td></td>
</tr>
<tr>
<td><strong>patients valid for the modified intention to treat analyses (N)</strong></td>
<td>887</td>
</tr>
<tr>
<td><strong>total VTE (n)</strong></td>
<td>100</td>
</tr>
<tr>
<td><strong>crude OR (95%CI)</strong></td>
<td>1 (ref)</td>
</tr>
<tr>
<td><strong>adjusted OR (95%CI)</strong></td>
<td>1 (ref)</td>
</tr>
<tr>
<td><strong>LR test</strong></td>
<td></td>
</tr>
</tbody>
</table>

VTE=venous thromboembolism; OR=Odds Ratio, LR test=Likelihood Ratio test for testing whether increase in glucose levels (in quartiles) has a significant influence on the occurrence of VTE. Total VTE is the composite of symptomatic VTE, asymptomatic DVT and all cause mortality.

*mmol/l
DISCUSSION

This study shows an association between stress-induced hyperglycaemia and total VTE in patients undergoing total hip arthroplasty. This was not observed in knee surgical patients, in whom only glucose levels prior to surgery were associated with total VTE.

An association between preoperatively elevated glucose levels and VTE in patients undergoing orthopaedic surgery has previously been reported. Mraovic and colleagues found that preadmission glucose levels exceeding 11.1 mmol/l independently increased the risk of pulmonary embolism (OR 3.19, 95%CI 1.25 to 8.10) when compared to glucose levels of less than 6.1 mmol/l in patients who underwent hip or knee arthroplasty. We did not find a relation between preoperative hyperglycaemia and VTE in patients undergoing hip surgery. However, 11.1 mmol/l is well above the cut-off value of the highest quartile in the hip surgery cohort, 8.0 mmol/l, and is likely to reflect patients with undiagnosed diabetes mellitus before surgery, a known risk factor for postsurgical complications. We also assessed the influence of post-surgical stress-induced glucose increase in relation to the development of VTE to investigate whether stress-hyperglycaemia is an independent risk factor for VTE following orthopaedic surgery.

Available pathophysiological evidence supports the relation between (acute) hyperglycaemia and hypercoagulability. In patients with diabetes mellitus, the concentration of several procoagulant factors are increased (fibrinogen, von Willebrand antigen, factor VII antigen, factor VIII) and antifibrinolytic factors are decreased, such as plasminogen activator inhibitor-1 (PAI-1). Furthermore, hip surgery has been shown to induce hyperglycaemia, which preceded a rise of factor VIII clotting activity, von Willebrand ristocetin cofactor activity, von Willebrand factor antigen and prothrombin fragment 1+2. In healthy volunteers, acute hyperglycaemia activates the coagulation system in an experimental setting.

In this study, only those patients in the highest quartile of post-surgical stress-induced hyperglycaemia were at increased risk for VTE, instead of a linear increase in risk. This implies that glucose levels apparently need to exceed a certain threshold to reach a significant association with VTE. Interestingly, the cut-off between the third and fourth quartiles in hip surgery patients, 7.9 mmol/l, is close to the classic cut-off for impaired glucose tolerance following the glucose tolerance test, 7.8 mmol/l.
Hyperglycaemia was not clearly associated with VTE in patients undergoing total knee replacement as in patients undergoing total hip replacement. This discrepancy cannot be explained by major differences in patients characteristics, as these were included as covariates in the regression model. The most important factor may concern the surgical procedure. Total knee replacement is performed with application of a tourniquet, occluding arterial and venous flow. Tourniquet use is related to the formation of thrombi. It is thus possible that the effect of hyperglycaemia is in part outweighed by other risk factors for VTE in patients undergoing total knee arthroplasty.

Although preoperative glucose samples were drawn at predefined time points, patients were not mandatory in the fasting state. We have, however, no reason to assume that there was a difference in distribution in fasting/non-fasting samples in patients with- or without VTE. Furthermore, this substudy involved a non-prespecified analysis. Nevertheless, we have investigated a prospective database, with a very large sample size. In addition, the most important assessments, VTE and glucose, were collected prospectively and comprehensively. The outcome “total VTE” not only included symptomatic VTE and asymptomatic DVT, but also “all cause mortality”. As the number of subjects who died during the treatment phase is very low in the four RECORD studies (n=23/8512, 0.3%), it is not likely that the inclusion of the latter outcome measure affected the results.

CONCLUSION

Stress-induced post-surgical hyperglycaemia is associated total VTE following total hip replacement. Likely due to the surgical procedure, this was not found in patients undergoing total knee arthroplasty. Future studies should assess whether the risk of VTE can be decreased by glucose lowering therapy in patients with stress-induced hyperglycaemia.
REFERENCES


Early postoperative hyperglycaemia is associated with postoperative complications after pancreatoduodenectomy

WJ Eshuis, J Hermanides, JW van Dalen, G van Samkar, ORC Busch, TM van Gulik, JH DeVries, JBL Hoekstra and DJ Gouma

Submitted for publication
ABSTRACT

**Background** Perioperative hyperglycaemia is associated with complications after various types of surgery. This relation was never investigated for pancreatoduodenectomy. Aim of this study was to investigate the relation between perioperative hyperglycaemia and complications after pancreatoduodenectomy.

**Methods** In a consecutive series of 330 patients undergoing pancreatodoudenectomy, glucose values were collected from the hospital information system during three periods: pre-, intra- and early postoperative. The average glucose value per period was calculated for each patient and divided in duals according to the median group value. Odds ratios for complications were calculated for the upper versus lower dual, adjusted for age, gender, ASA-classification, BMI, diabetes mellitus, intraoperative blood transfusion, duration of surgery, intraoperative insulin administration and octreotide use. The same procedures were carried out to assess the consequences of increased glucose variability, expressed by the standard deviation.

**Results** Average glucose values were 7.5 (preoperative), 7.4 (intraoperative) and 7.9 mmol/l (early postoperative). Pre- and intraoperative glucose values were not associated with postoperative complications. Early postoperative hyperglycaemia (>7.8 mmol/l) was significantly associated with complications (OR 2.9, 95%CI 1.7 to 4.9). Overall, high glucose variability was not significantly associated with postoperative complications, but early postoperative patients who had both high glucose values and high variability had an OR for complications of 3.6 (95%CI 1.9 to 6.8) compared to the lower glucose dual.

**Conclusions** Early postoperative hyperglycaemia is associated with postoperative complications after pancreatoduodenectomy. High glucose variability may enhance this risk. Future research must demonstrate whether strict glucose control in the early postoperative period prevents complications after pancreatoduodenectomy.
INTRODUCTION

Although mortality of pancreateoduodenectomy (PD) is well below 5% in high volume centres, complications occur in up to 50% of patients. Most prevalent surgical complications include delayed gastric emptying, leakage of pancreaticojejunostomy or hepaticojejunostomy and infectious complications. Complications that are not directly related to surgery are mostly of cardiac, pulmonary or urogenital origin.1-4 Numerous studies have been carried out to identify risk factors for the development of complications after PD. Factors reported to be associated with morbidity after PD include high body mass index, diabetes mellitus, high preoperative blood urea nitrogen and low preoperative serum albumin, longer duration of surgery, intraoperative blood transfusion and a small, non-dilated main pancreatic duct.5-11 Higher perioperative glucose levels have been shown to be associated with complications after various types of cardiac, general, vascular and orthopaedic surgery.12-18 This effect is generally attributed to an impaired immune response, in combination with an excessive release of stress hormones and inflammatory cytokines resulting in diminished insulin action.12;15;17 However, perioperative hyperglycaemia does not increase postoperative morbidity in all types of surgery: in oesophageal resection no relation was found between early postoperative hyperglycaemia and postoperative complications.19 The relation between perioperative glucose levels and postoperative complications after PD has never been investigated. Apart from surgical stress hyperglycaemia, patients undergoing PD might be extra susceptible to disarrangement of glucose levels: pancreatic cancer - the main indication for PD - is associated with progressive hyperglycemia and (new onset) diabetes mellitus in 20% to 30% of patients before diagnosis.20-22 The operation itself involves manipulation and resection of pancreatic tissue, and resection of the duodenum, one of the enteric regions where the incretin hormone GIP (glucose-dependent insulino tropic polypeptide) is released, which assists in maintaining glucose homeostasis. Together, this may render patients hyperglycaemic.23;24 Aiming for near-normal glucose levels (4.4 to 6.1 mmol/l) in a surgical intensive care unit (ICU) significantly reduced mortality.25 Although subsequent studies on such strict glucose control has yielded conflicting results in various populations, it seems to reduce mortality and morbidity in surgical ICU patients.26 Because patients undergoing PD are at risk for hyperglycaemia, it seems important to establish whether increased perioperative glucose levels are associated with poor
outcome, especially since strict glucose control may be beneficial in this population.26 The aim of the present study was therefore to investigate the association of perioperative glucose levels with postoperative complications after PD.
Early postoperative hyperglycaemia is associated with complications after PD

METHODS

Patients and study outline
In a consecutive series of 330 patients undergoing elective PD between July 2000 and December 2006 for suspected pancreatic or periampullary malignancy, clinicopathologic data, demographics and postoperative outcomes were prospectively registered. Glucose values were analysed retrospectively. Since the present study involved a retrospective analysis of anonymised data, the Dutch Ethical Review Board regulations do not require informed consent.

Surgical Procedure
The standard surgical procedure was the pylorus-preserving PD with removal of lymph nodes at the right side of the portal vein, as earlier described. In case of tumor ingrowth in pylorus or duodenum, a classic Whipple’s resection was performed. If minimal tumor ingrowth in the portal or superior mesenteric vein was found, a segmental or wedge resection was carried out. Reconstruction was performed by retrocolic hepaticojejunostomy and pancreaticojejunostomy and retrocolic or antecolic duodenojejunostomy, without Roux-Y reconstruction. One silicone drain was left in the foramen of Winslow near the hepaticojejunostomy and pancreaticojejunostomy. Feeding jejunostomy was not standard. Octreotide was routinely administered for 7 days until 2002, and afterwards on indication of soft pancreatic tissue or small pancreatic duct. Postoperatively, patients stayed at the recovery room until the morning of the first postoperative day, before returning to the surgical ward.

Measures of glucose
The most recent venous plasma glucose level within 4 months before surgery was collected from the clinical information system or patient chart. Details about fasting or non-fasting state were mostly unknown. All available intraoperative and early postoperative glucose values (from operation until the end of the first postoperative day) were collected. During surgery and in the early postoperative period (defined as the period at the recovery room, or in case of extended stay at the recovery room, until postoperative day 1), all blood glucose values were fasting. They were measured by a blood gas/pH analyzer (Ciba Corning 865, Chiron Diagnostics, Medford, MA, USA) in blood samples obtained from an arterial catheter, and automatically stored in the hospital information system. We calculated the mean intraoperative and early postoperative glucose value per
patient. Furthermore, as a measure of glucose variability, the standard deviations (SD) of intraoperative and early postoperative glucose values in each patient were calculated.

**Outcome measures**

Primary outcome measure was whether the patient experienced any postoperative complication. All surgical complications and non-surgical complications were taken into account.

Secondary outcome measures were the occurrence of a surgical complication, the occurrence of an infectious complication, a score of IIIa or higher in the Dindo-Clavien classification of complications, delayed gastric emptying and pancreaticejejunostomy leakage (grade B or C according to the International Study Group of Pancreatic Surgery criteria), relaparotomy, admission to intensive or medium care unit or readmission to the recovery room, length of hospital stay, and hospital readmission within 30 days.\(^{30-32}\)

**Statistical analyses**

Results are presented as mean ± SD or median with interquartile range (IQR), depending on the distribution of the data.

All glucose variables (the preoperative value, mean and SD of intraoperative and early postoperative values) were divided into duals of equal group size. Using multivariate binary logistic regression, we calculated Odds Ratios (OR) for all dichotomous outcome measures for patients in the upper versus the lower dual. Correlation with length of hospital stay (Natural log (Ln)-transformed) was calculated using linear regression. Calculations were carried out separately for each period (preoperative, intraoperative and early postoperative). Analyses were adjusted for age, gender, ASA-classification, body mass index (BMI), diabetes mellitus, intraoperative blood transfusion, duration of surgery, intraoperative insulin administration and octreotide use. Analyses of SD were also adjusted for the mean glucose value in the respective period.

Finally, secondary outcomes analyses were corrected for multiple testing according to Benjamini and Hochberg.\(^ {33}\) \(p\)-values below 0.05 were considered statistically significant. All analyses were performed in SPSS version 16.0 (SPSS Inc., Chicago, IL, USA).
RESULTS

Patient population
Patient and operative characteristics are summarised in Table 1. Mean age of the cohort was 62 (SD 12); 56% was male and 16% had diabetes mellitus. A preoperative glucose value was available in 79% of patients. At least one intraoperative glucose value was available in 97% of patients and at least one early postoperative glucose value was available in 99% of patients (Table 2).

Table 1-baseline and operative characteristics of 330 patients undergoing pancreatoduodenectomy in the period July 2000 – December 2006

<table>
<thead>
<tr>
<th>Baseline characteristics</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years (mean, SD)</td>
<td>62.3</td>
</tr>
<tr>
<td>Male sex, n (%)</td>
<td>185</td>
</tr>
<tr>
<td>ASA I, n (%)</td>
<td>58</td>
</tr>
<tr>
<td>ASA II, n (%)</td>
<td>209</td>
</tr>
<tr>
<td>ASA III, n (%)</td>
<td>63</td>
</tr>
<tr>
<td>Body Mass Index, n (%)</td>
<td></td>
</tr>
<tr>
<td>- Underweight (&lt;18.5)</td>
<td>19</td>
</tr>
<tr>
<td>- Normal weight (18.5 – 24.9)</td>
<td>173</td>
</tr>
<tr>
<td>- Overweight (25 – 29.9)</td>
<td>120</td>
</tr>
<tr>
<td>- Obese (30 or higher)</td>
<td>18</td>
</tr>
<tr>
<td>Diabetes Mellitus, n (%)</td>
<td>53</td>
</tr>
<tr>
<td>Underlying disease, n (%)</td>
<td></td>
</tr>
<tr>
<td>- Pancreatic adenocarcinoma</td>
<td>103</td>
</tr>
<tr>
<td>- Ampullary adenocarcinoma</td>
<td>77</td>
</tr>
<tr>
<td>- Distal CBD adenocarcinoma</td>
<td>43</td>
</tr>
<tr>
<td>- Other (pre)malignant</td>
<td>58</td>
</tr>
<tr>
<td>- Chronic pancreatitis</td>
<td>32</td>
</tr>
<tr>
<td>- Other benign</td>
<td>17</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Operative characteristics</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Operative time, minutes (median, IQR)</td>
<td>280</td>
</tr>
<tr>
<td>Blood transfusions, n (%)</td>
<td></td>
</tr>
<tr>
<td>- None</td>
<td>259</td>
</tr>
<tr>
<td>- 1-3</td>
<td>59</td>
</tr>
<tr>
<td>- 4 or more</td>
<td>12</td>
</tr>
<tr>
<td>Pylorus preserved, n (%)</td>
<td>299</td>
</tr>
</tbody>
</table>

SD, standard deviation; ASA, American Society of Anesthesiologists; CBD, common bile duct; IQR, interquartile range
Mean preoperative glucose was 7.5 (SD 4.2) mmol/l and mean intraoperative glucose 7.4 (SD 1.9) mmol/l. Intraoperative insulin was administered in 14% of patients. During stay at recovery, mean glucose was significantly higher as compared to the intraoperative period: 7.9 (SD 1.5) mmol/l ($p<0.001$, paired t-test, Figure 1).

![Figure 1- mean glucose values pre-, intra-, and early postoperative](image-url)

**Table 2** - perioperative glucose values of 330 patients undergoing pancreatoduodenectomy

<table>
<thead>
<tr>
<th>Moment of sampling</th>
<th>Preoperative</th>
<th>Intraoperative</th>
<th>Early postoperative</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>-Preoperative value available, n (%)</td>
<td>259 (79)</td>
<td>320 (97)</td>
</tr>
<tr>
<td></td>
<td>-Preoperative value, mmol/l* (mean, SD)</td>
<td>7.5 (4.2)</td>
<td>7.4 (1.9)</td>
</tr>
<tr>
<td></td>
<td>-At least 1 value available, n (%)</td>
<td>320 (97)</td>
<td>263 (80)</td>
</tr>
<tr>
<td></td>
<td>-&gt;1 value available, n (%)</td>
<td>263 (80)</td>
<td>263 (80)</td>
</tr>
<tr>
<td></td>
<td>-No. of samples per patient (mean, SD)</td>
<td>2.9 (1.6)</td>
<td>1.0 (1.2)</td>
</tr>
<tr>
<td></td>
<td>-Intraoperative value, mmol/l (mean, SD)</td>
<td>7.4 (1.9)</td>
<td>1.0 (1.2)</td>
</tr>
<tr>
<td></td>
<td>-Standard deviation mmol/l (mean, SD)</td>
<td>1.0 (1.2)</td>
<td>1.0 (1.2)</td>
</tr>
</tbody>
</table>

SD, standard deviation

**Figure 1**- mean glucose values pre-, intra-, and early postoperative
Postoperative morbidity was 58%. Surgical complications occurred in 48% of patients; most prevalent complications were delayed gastric emptying and pancreaticojejunalostomy leakage (Table 3); 83 patients (25%) had a complication of grade IIIa or higher in the Dindo-Clavien classification (Table 4). There were no significant differences in complications in patients with or without diabetes (Table 5).

**Table 3**-postoperative complications and other outcomes in 330 patients undergoing pancreatoduodenectomy

<table>
<thead>
<tr>
<th>Complication</th>
<th>Any complication, n (%)</th>
<th>Surgical complications, n (%)</th>
<th>Delayed gastric emptying (ISGPS grade B or C)</th>
<th>Pancreaticojejunalostomy leakage (ISGPS grade B or C)</th>
<th>Postpancreatectomy hemorrhage (ISGPS grade B or C)</th>
<th>Hepaticojejunalostomy leakage</th>
<th>Intra-abdominal abscess (without PJ- or HJ-leakage)</th>
<th>Wound infection</th>
<th>Other</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any complication, n (%)</td>
<td>191 (58)</td>
<td>158 (48)</td>
<td>99 (30)</td>
<td>52 (16)</td>
<td>17 (5)</td>
<td>11 (3)</td>
<td>10 (3)</td>
<td>43 (13)</td>
<td>45 (14)</td>
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<tr>
<td>Surgical complications, n (%)</td>
<td></td>
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<tr>
<td>Delayed gastric emptying (ISGPS grade B or C)</td>
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<tr>
<td>Pancreaticojejunalostomy leakage (ISGPS grade B or C)</td>
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<tr>
<td>Postpancreatectomy hemorrhage (ISGPS grade B or C)</td>
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<tr>
<td>Hepaticojejunalostomy leakage</td>
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<td></td>
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<tr>
<td>Intra-abdominal abscess (without PJ- or HJ-leakage)</td>
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<tr>
<td>Wound infection</td>
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<td></td>
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<td></td>
<td></td>
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<tr>
<td>Other</td>
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</tbody>
</table>

**Table 4**-classification of 330 patients undergoing pancreatoduodenectomy according to the Clavien-Dindo classification of complications

<table>
<thead>
<tr>
<th>Clavien-Dindo grade, n (%)</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>0 – No complication</td>
<td>121 (37)</td>
</tr>
<tr>
<td>I – No pharmacologic treatment or intervention needed*</td>
<td>21 (6)</td>
</tr>
<tr>
<td>II – Requiring pharmacological treatment†</td>
<td>105 (32)</td>
</tr>
<tr>
<td>IIIa – Requiring intervention – not under general anesthesia</td>
<td>35 (11)</td>
</tr>
<tr>
<td>IIIb – Requiring intervention – under general anesthesia</td>
<td>3 (1)</td>
</tr>
<tr>
<td>IVa – Life-threatening complication requiring MC/IC management, single organ dysfunction</td>
<td>34 (10)</td>
</tr>
<tr>
<td>IVb – As IVa, but with multiple organ dysfunction</td>
<td>3 (1)</td>
</tr>
<tr>
<td>V – Death</td>
<td>8 (2)</td>
</tr>
</tbody>
</table>

* Allowed: antiemetics, antipyretics, analgetics, diuretics, electrolytes, physiotherapy, wound infections opened at bedside
† Includes blood transfusions and total parenteral nutrition
Table 5 - distribution of glucose levels and complications after 330 pancreatoduodenectomies in patients without diabetes and patients with diabetes

<table>
<thead>
<tr>
<th></th>
<th>Preoperative</th>
<th>Intraoperative</th>
<th>Early postoperative</th>
<th>Any complication*</th>
</tr>
</thead>
<tbody>
<tr>
<td>No diabetes (n=277)</td>
<td>6.5 (2.1)</td>
<td>7.1 (1.4)</td>
<td>7.9 (1.4)</td>
<td>165 (59.6)</td>
</tr>
<tr>
<td>Diabetes (n=53)</td>
<td>11.5 (7.2)</td>
<td>8.7 (3.3)</td>
<td>8.2 (2.1)</td>
<td>26 (49.1)</td>
</tr>
</tbody>
</table>

Glucose values in mmol/l, results presented as mean (SD).

* Chi-squared test for between group difference in any complication $p = 0.16$

**Perioperative glucose values and postoperative complications**

Preoperative and mean intraoperative glucose values were not associated with the occurrence of a postoperative complication (Figure 2). In the early postoperative period, a higher mean glucose (>7.8 mmol/l) was significantly associated with postoperative complication (OR 2.9, 95% CI 1.7 to 4.9) (Figure 2). A Receiver-Operator-Characteristic curve (ROC-curve) showed that a cut-off point of 7.8 mmol/l was the best discriminative value for the occurrence of a postoperative complication, with a sensitivity of 0.58 and a specificity of 0.63 (curve not shown).

High glucose variability during operation or in the early postoperative period was not associated with the occurrence of a postoperative complication. Patients in the upper dual for both mean glucose value and glucose variability in the early postoperative period had an OR for the development of a postoperative complication of 3.6 (95% CI 1.9 to 6.8) compared to the lower glucose dual.

**Secondary outcome measures**

Preoperative and mean intraoperative glucose values were not associated with any of the secondary outcome measures (Figure 2). A higher mean early postoperative glucose value was significantly associated with surgical and infectious complications (ORs 2.0, 95% CI 1.2 to 3.2, and 2.3, 95% CI 1.4 to 3.8, respectively), delayed gastric emptying (OR 2.1, 95% CI 1.2 to 3.7), Dindo-Clavien complication score >=III (OR 2.3, 95% CI 1.3 to 4.3), and relaparotomy (OR 6.1, 95% CI 1.6 to 24.1). Length of stay was 1.2 days (95% CI 1.1 to 1.4, $p=0.01$) longer in the upper dual. High glucose variability intraoperatively or in the early postoperative period was not associated with any of the secondary outcome measures.
**Figure 2A** - Odds ratios (ORs) for all outcomes comparing patients with preoperative glucose of >=6.30 mmol/l to patients <6.30 mmol/l. After correction for multiple testing, none of the ORs were significant. ICU= Admission to intensive care unit, medium care unit or readmission to the recovery room. PJ, pancreaticojejunostomy leakage; DGE, delayed gastric emptying.

**Figure 2B** - Odds ratios (ORs) for all outcomes comparing patients with intraoperative glucose of >=7.06 mmol/l to patients <7.06 mmol/l. After correction for multiple testing, none of the ORs were significant. ICU= Admission to intensive care unit, medium care unit or readmission to the recovery room. PJ, pancreaticojejunostomy leakage; DGE, delayed gastric emptying.

**Figure 2C** - Odds ratios (ORs) for all outcomes comparing patients with early postoperative glucose of >=7.78 mmol/l to patients <7.78 mmol/l. "p" values are adjusted for multiple testing. ICU= Admission to intensive care unit, medium care unit or readmission to the recovery room. PJ, pancreaticojejunostomy leakage; DGE, delayed gastric emptying.
DISCUSSION

In this study we showed that early postoperative hyperglycaemia (>7.8 mmol/l) after pancreatoduodenectomy was significantly associated with the development of a postoperative complication, possible confounders taken into account. This was reflected by a higher risk of surgical and infectious complications, delayed gastric emptying, Dindo-Clavien complication score >=III and relaparotomy. Also length of stay was significantly longer in these patients. When elevated postoperative glucose was accompanied by high glucose variability, the risk of a postoperative complication seemed to increase. These novel findings were all adjusted for age, gender, ASA-classification, BMI, diabetes mellitus, intraoperative blood transfusion, duration of surgery, intraoperative insulin administration and use of octreotide. Mean glucose levels before and during PD were comparable and significantly lower as compared to early postoperative levels. Elevated preoperative and intraoperative glucose and higher glucose variability were not associated with the development of complications.

Our findings that early postoperative higher glucose levels are associated with complications after PD are in line with previous studies investigating this relation in other types of surgery. Ramos and coworkers identified postoperative hyperglycaemia as a significant risk factor for postoperative infections in general and vascular surgery. Vriesendorp et al observed an OR of 5.1 (95% CI 1.6 to 17.1) for postoperative infections when early postoperative glucose values were 8.4 mmol/l or above in peripheral vascular surgery. Also the seemingly additional detrimental effect of high glucose variability was described before in populations of critically ill and surgical intensive care unit patients. Although it is difficult to elucidate whether hyperglycaemia results from postoperative complications or indeed contributes to their development, we believe the latter mechanism is might be most plausible, but should be proven in the future by early regulation and control. As the increase in glucose levels preceded the development of complications and possible confounders were accounted for in the analyses, a causal relation between elevated glucose levels postoperatively and the development of complications is suspected.

Early postoperative hyperglycaemia was associated with the most prevalent complication in our cohort, delayed gastric emptying. Besides being a common complication after pancreatoduodenectomy, gastroparesis is a well-known complication of longstanding diabetes mellitus. It has also been associated with acute hyperglycaemia.
Several explanations for the harmful effects of both stress hyperglycaemia and glucose variability have been proposed, such as glucose toxicity and oxidative stress, stimulating intracellular pathways that lead to detrimental tissue effects such as mitochondrial dysfunction and immune dysregulation. Although the application of strict glucose control has led to conflicting results in a variety of populations, a recent meta-analysis suggests that surgical ICU patients benefit from strict glucose control. Okabayashi and coworkers recently showed that strict control of perioperative blood glucose following pancreatic resection is possible, and may reduce postoperative infection rates.

We found that in PD, intraoperative glucose levels were comparable to preoperative levels, and that pre- and intraoperative glucose values and variability were not a risk factor for postoperative complications after PD. Intraoperative glucose values have earlier been described as risk factor for adverse outcomes in cardiac surgery and liver transplantation. Contrary to PD, these operations involve substantial ischemia and reperfusion injury, which may explain these seemingly contradictory different findings.

Interestingly, the mean glucose in patients with diabetes decreased after surgery as compared to the intraoperative values, indicating a different glucose response to surgery. Diabetes patients did not have more complications than non-diabetes patients in our series, whereas diabetes mellitus has been described as a risk factor for intra-abdominal complications after PD. Our cohort was however too small to draw firm conclusions about the diabetes subpopulation.

Using an ROC-curve analysis we found that the cut-off value of 7.8 mmol/l early postoperatively was the most discriminatory value when predicting complications. This was comparable to our population mean and median value. Perhaps not coincidentally, normal healthy subjects will not peak above 7.8 mmol/l when challenged with oral glucose, supporting the strength of this cut-off value.

Our study was limited by the retrospective collection of glucose values. Preoperative values were not available in 21% of patients. However, postoperative morbidity in these patients was not different from patients who did have a preoperative value available (59% versus 58%, data not shown). Glucose sampling was not standardised, leading to differences in timing, amount and indication of glucose samples. To minimise these sources of error, the average glucose value per period was taken. Also, intraoperative and postoperative glucose values were available in nearly all patients, showing that frequent perioperative sampling was common, irrespective of the condition of the patient.
Our study is the first to investigate the effect of perioperative glucose levels in this specific patient group with pancreatic disease. It was performed in a large consecutive series of elective patients. Patient characteristics and hospital course were prospectively scored.

In conclusion, early postoperative glucose levels above 7.8 mmol/l are significantly associated with postoperative complications after PD. Future research must clarify the underlying mechanisms and pathways of this relation. Treatment of hyperglycaemia is possible and strict glucose control may be favourable in surgical patients. A randomised clinical trial should be conducted to investigate whether a strategy of strict glucose control (versus glucose correction on indication) in the early postoperative period is beneficial in this patient group.
REFERENCES


Early postoperative hyperglycaemia is associated with complications after PD


PART II

DETECTION AND TREATMENT OF HYPERGLYCAEMIA
ABSTRACT

Continuous subcutaneous glucose monitoring (CGM) is a developing technology in the treatment of diabetes mellitus. The first randomised controlled trials on its efficacy have been performed. In several studies, CGM lowered HbA1c in adult patients with suboptimally type 1 diabetes mellitus, when selecting compliant patients who tolerate the device. However, as a preventive tool for hypoglycaemia, CGM has not fulfilled the great expectations. Increasing reimbursement of CGM is expected in the near future, awaiting studies on cost-effectiveness.
INTRODUCTION

Pioneering work of artificially replacing the glucose-monitoring function of the pancreas started in the 1970s.\textsuperscript{1} With the introduction of the microdialysis technique in the early 1990s, the future of continuous subcutaneous glucose monitoring (CGM) seemed bright and shiny.\textsuperscript{2,3} The great expectation was that, by providing the patient with a continuous stream of data and alarms for otherwise unrecognised (nocturnal) hypo- and hyperglycaemia, the HbA\textsubscript{1c} target of <7% was in reach and the main barrier to effective diabetes treatment—the occurrence of severe hypoglycaemia—could be overcome.\textsuperscript{4-6} Even more, integrating CGM and continuous subcutaneous insulin infusion (CSII) would mean it would be a matter of time before the closed-loop system would be available.\textsuperscript{7} Several years later, the first needle-type sensor became clinically available, though it could only be read out retrospectively.\textsuperscript{8} Currently, there are three real-time CGM systems on the market that are approved by the US Food and Drug Administration (FDA) and have the Conformité Européenne (CE) mark: the Freestyle Navigator (Abbott Diabetes Care, Alameda, CA, USA); the Guardian Real-Time (Medtronic MiniMed, Northridge, CA, USA); and the DexCom SEVEN (DexCom, San Diego, CA, USA; only available in the USA). All these systems measure glucose in the subcutaneous tissue and provide real-time glucose measurements every 1 to 5 min. The first randomised controlled trials (RCTs) have now been performed with real-time CGM, prompting the next questions: did the sensor fulfil expectations and is this reflected in the current reimbursement status of the device?

EFFECT ON HbA\textsubscript{1c}

The first RCT, performed by Deiss and colleagues, investigated a needle-type continuous subcutaneous glucose monitor in patients with poorly controlled type 1 diabetes (HbA\textsubscript{1c} >=8.1% on intensive treatment).\textsuperscript{9} There was a difference in HbA\textsubscript{1c} reduction of 0.6% after 3 months in favour of patients who were instructed to use the device continuously, as compared with patients using conventional treatment. In a third arm, patients used CGM biweekly, and this did not result in a significant HbA\textsubscript{1c} improvement. A subsequent 26 week randomised treat-to-target study performed by Hirsch and coworkers (the STAR 1 trial) yielded disappointing results.\textsuperscript{10} There was no significant difference in change in HbA\textsubscript{1c} between type 1 diabetes patients using CSII randomised to either augmenting their current therapy with CGM or continuing with their standard self-monitoring of blood
glucose (SMBG). In both groups, there was a decrease in HbA1c of 0.6 to 0.7%. That the decreases in HbA1c were comparable in both groups was attributed to intensification of the treatment in both the control and intervention groups. It seems that in an attempt to assure equal attention times in both groups, the control group was treated more intensively than would be feasible in daily practice. In the Juvenile Diabetes Research Foundation (JDRF) study, three different age groups (25, 15 to 24 and 8 to 14 years) were randomised to either CGM or SMBG continuation.11 All patients had type 1 diabetes and the vast majority were already using CSII. The mean difference in HbA1c change was 0.5% after 26 weeks in favour of patients using CGM, but this was only in those aged 25 years and older. No significant difference in HbA1c change was detected in the other age groups. In both the STAR 1 and the JDRF trials, the frequency of sensor usage was strongly correlated to the decrease in HbA1c. This is in line with the study from Deiss et al.9 and the recently published RealTrend study12. In this latter study, patients administering multiple daily injections and with an HbA1c $\geq$8% at inclusion started with either CSII therapy or sensor-augmented pump therapy for 26 weeks. From a predefined analysis, HbA1c improved compared with the CSII group only in patients using the sensor $>70\%$ of the time. Unfortunately, patients in the sensor-augmented pump group had already used CGM for 9 days before the baseline HbA1c measurement was performed and therefore the observed HbA1c difference, 0.41%, may have been underestimated. The combination of CGM and CSII has also been investigated in the recently presented Eurythmics trial, where a difference in HbA1c improvement of 1.21% in favour of the sensor-augmented pump group was found when type 1 diabetes patients (HbA1c at entry $\geq$8.2%), who were using multiple daily injection therapy and SMBG, were randomised to continuing their current therapy or starting CGM-augmented insulin-pump therapy.13 It is interesting that the JDRF trial and the Eurythmics trial, both showing a significant HbA1c improvement in the intervention group, confronted patients with a short period of blinded CGM usage at baseline before randomisation. Patients who did not tolerate the device, and therefore would be likely to drop out or be non-compliant during the study course, were at least partly filtered out before randomisation.

**EFFECT ON SEVERE HYPOGLYCAEMIA**

The improvement in HbA1c in the different RCTs was not accompanied by a significant increase in severe hypoglycaemia.9,11-13 This seems reassuring, but
CGM did not fulfil the expectation that its use would reduce the frequency of severe hypoglycaemic events. Even more, in the STAR 1 trial, the use of CGM was associated with a significant increase in severe hypoglycaemia. This is most likely related to the reduced awareness of auditory and vibratory alarms during hypoglycaemia and non-use of the device during high-risk activities, such as intensive sports. No study so far has shown a decrease in the frequency of severe hypoglycaemia in a CGM arm as compared with the control arm in type 1 diabetes. Indeed, sensors have an inaccuracy of up to 21% when comparing plasma glucose values with subcutaneous glucose values. This inaccuracy is even more pronounced in the hypoglycaemic range. In addition, the usefulness of the CGM devices for detecting forthcoming hypoglycaemia is limited by a putative physiological delay between the blood glucose and glucose concentration in the subcutaneous tissue, which is accompanied by an instrumental delay of the sensor. In other words, patients need more time to prevent hypoglycaemia, especially when they have hypoglycaemia unawareness. Perhaps the developing technology will result in an alarm function for predicting hypoglycaemia by using the rate of change in glucose in the lower euglycaemic range. For now, CGM is insufficient for the prevention of severe hypoglycaemia.

COSTS AND REIMBURSEMENT

Interestingly, it is the argument of possibly preventing severe hypoglycaemia that has persuaded healthcare organisations in Israel to reimburse CGM use. Children with type 1 diabetes who have experienced more than two severe hypoglycaemic episodes within 1 year are entitled to CGM compensation. In addition, real-time CGM is now covered by the majority of health plans in the USA, including the federal Medicare program. Reimbursement is generally available for type 1 patients with severe hypoglycaemia or those who are not meeting American Diabetes Association HbA1c targets. In the Netherlands and part of Italy, retrospective CGM is currently reimbursed. The Czech Republic covers up to four sensors per year for retrospective CGM and in Sweden, real-time CGM is reimbursed for patients using CSII and having two or more severe hypoglycaemic episodes per year, children who require at least ten plasma glucose tests per 24 h and patients with HbA1c >10% while receiving optimised insulin therapy. The reimbursement indication of hypoglycaemia illustrates that so far, coverage was based on feeling rather than the (scarce) evidence. This is not to say that CGM is not able to reduce severe hypoglycaemia, but we need randomised trials in patients.
at high risk for severe hypoglycaemia (i.e. those suffering from hypoglycaemia unawareness). From the results of the clinical trials to date, we can now argue that CGM offers a clear health benefit, expressed as HbA1c lowering, for type 1 diabetes patients with HbA1c values above 8%. The additional costs for sensors are US$4380 per person year compared with US$550-2740 when using SMBG. Consequently, we need to calculate whether the long-term health benefits of CGM following from ascertained lowering of HbA1c outweigh the costs when compared with standard care with multiple daily injections and/or insulin pumps. A similar comparison was performed by Roze and colleagues indicating that the cost-effectiveness of CSII is acceptable. A technical appraisal from the National Institute for Health and Clinical Excellence (England and Wales) seems timely.

OTHER PATIENT GROUPS

The application of CGM in patient groups other than those with type 1 diabetes is limited. No trials with adequate duration assessing HbA1c change have been performed for patients with type 2 diabetes. One particular patient group that warrants special attention is pregnant women with diabetes. CGM has proven effective in improving glucose control at the end of pregnancy. It resulted in fewer cases of macrosomia in the offspring, with an odds ratio of 0.36 (95% CI 0.13 to 0.98). As it concerns a limited time span, reimbursement of CGM in this group should impose no significant financial burden on the healthcare system. Finally, the use of CGM for treating in-hospital hyperglycaemia could be valuable, and the first randomised studies are awaited. However, the advantage of CGM in this setting may be less evident, as frequent blood sampling is standard practice in the intensive care unit and CGM accuracy may suffer if the circulation is compromised.

CONCLUSION

CGM with or without CSII has been proven to lower HbA1c in adult patients with type 1 diabetes mellitus and HbA1c values above 8%, when compliant patients who tolerate the device are selected. However, CGM is not the final answer to severe hypoglycaemia. Awaiting a cost-effectiveness analysis, increasing reimbursement of CGM is expected.
ACKNOWLEDGMENTS

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Sensor augmented pump therapy lowers HbA$_{1c}$ in suboptimally controlled type 1 diabetes; a randomised controlled trial

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Submitted for publication
ABSTRACT

Aims To investigate the efficacy of sensor augmented pump therapy vs. multiple daily injection therapy in patients with suboptimally controlled type 1 diabetes.

Methods In this investigator initiated multicentre trial (Eurythmics Trial) in 8 outpatient centres in Europe we randomised 83 Diabetes type 1 patients (40 woman) currently treated with multiple daily injections, age 18-65 years and haemoglobin A1c (HbA1c)\(>=8.2\%\) to 26 weeks of treatment with either a sensor augmented insulin pump (SAP, n=44) (Paradigm\textsuperscript{®} REAL-Time) or multiple daily injections (MDI, n=39). Change in HbA1c between baseline and 26 weeks, sensor derived endpoints and patient reported outcomes were assessed.

Results In the SAP group 43/44 (98\%) patients completed the trial and in the MDI group 35/39 (90\%). Mean HbA1c at baseline and 26 weeks changed from 8.46\% (SD 0.95) to 7.23\% (SD 0.65) in the SAP group and from 8.59\% (SD 0.82) to 8.46\% (SD 1.04) in the MDI group. Mean difference in change in HbA1c after 26 weeks was -1.21\% (95\% confidence interval -1.52 to -0.90, \(p<0.001\)) in favour of the SAP group. This was achieved without an increase in percentage of time spent in hypoglycaemia: between-group difference 0.0\% (95\% confidence interval -1.6 to 1.7, \(p=0.96\)). Problem Areas In Diabetes and Diabetes Treatment Satisfaction Questionnaire scores improved in the SAP group.

Conclusions Sensor augmented pump therapy effectively lowers HbA1c in type 1 diabetes patients suboptimally controlled on MDI

Clinical Trial Registration controlled-trials.com ISRCTN22472013
INTRODUCTION

Intensive treatment of type 1 diabetes mellitus has become the standard of care since it reduces diabetes-related complications marked by haemoglobin A$_1c$ (HbA$_1c$) reduction$^1$. However, many patients do not reach the HbA$_1c$ target of $<7\%$.$^2$ Achieving euglycaemia is limited by symptomatic hypoglycaemia and undetected hypo- and hyperglycaemia.$^3$-$^5$ With technical developments, continuous subcutaneous insulin infusion (CSII) and continuous subcutaneous glucose monitoring (CGM) have become available, providing more flexible insulin dosing schemes and a continuous stream of glucose data.$^6$-$^7$ Indeed, recent meta-analyses indicate that CSII is effective in lowering HbA$_1c$ in patients with high HbA$_1c$ at start and in reducing severe hypoglycaemia in patients at risk.$^8$-$^{10}$ The Juvenile Diabetes Research Foundation trial found a difference in change in HbA$_1c$ of -0.5% in favour of CGM treated type 1 diabetes patients, as compared to a control group performing self measurement of blood glucose (SMBG).$^{11}$ Recently, an integrated real-time CGM and insulin pump system has entered the market, with alarm function for hypo- and hyperglycaemia and a mealtime bolus advisor (Paradigm REAL-Time System; Medtronic MiniMed, Inc., Northridge, CA).$^{12}$ Today, this integrated platform is the most extensive technical support one can provide to diabetes patients, without taking over some parts of patient self-control, the next step towards the closed-loop or artificial pancreas.$^{13}$ It could have potential for patients failing on intensive optimised treatment with multiple daily injections (MDI) and SMBG. As with any new device, it needs to be compared to standard care to evaluate efficacy. Therefore we compared sensor augmented pump therapy to intensive multiple daily injection therapy in suboptimally controlled type 1 diabetes mellitus patients in a randomised controlled multicentre trial.

METHODS

Study Design and Patient Population

This was a 26-week open-label, multinational, multi-centre randomised controlled clinical trial, performed between April 2007 and January 2009 in 8 centres experienced in clinical research and pump therapy. Centres qualified for the trial after being able to verify sensor augmented insulin-pump experience with at least three type 1 diabetes patients for a treatment period of two weeks.
Eligible patients were aged 18 to 65 years, diagnosed with type 1 diabetes at least 1 year prior to study participation, currently treated with optimised multiple daily injections, but having an HbA1c >=8.2% at screening, despite repeated attempts to improve this by re-education, including the availability insulin pump therapy. This cut-off for HbA1c was chosen because it represents the median HbA1c in the DCCT-EDIC cohort. Patients treated with human insulin could also be included if analogues had been tried in the past.

Exclusion criteria were hearing problems or impaired vision that might hinder recognition of alarms, substance abuse other than nicotine, abdominal skin abnormalities that might hinder subcutaneous insertion, current treatment for any psychiatric disorder other than depression, treatment with CSII in the six months prior to study entry, pregnancy, heart failure, cancer or kidney disease, and participation in another therapeutic study. The study was approved by the ethics committees of all participating centres and performed in accordance with the declaration of Helsinki and Good Clinical Practice. All patients provided written informed consent. Quality of the data was monitored by the Academic Medical Centre (AMC) Clinical Research Unit, Amsterdam. The study is registered with controlled-trials.com, ISRCTN22472013, as the EURopean (Y) Trial to lower HbA1c by Means of an Insulin pump augmented by a Continuous glucose Sensor (Eurythmics trial).

**Study Procedures**

The study flowchart is provided in Figure 1. Prior to randomisation, participants underwent 6 days of CGM measurements (Guardian® REAL-Time Clinical, Medtronic MiniMed, Inc., Northridge, CA), without visible sensor values or alarms. Treatment advice was given based on the downloaded data to optimise therapy at start in all patients. Hereafter, patients were randomised to receive either 26 weeks of treatment with a sensor augmented insulin pump (SAP) or standard care with continuation of MDI therapy, optimised by the advice derived from the preceding 6 days of CGM. Randomisation was stratified per centre in computer generated sequences unknown to the investigator. Via a secured internet database (Oracle Corporation, Redwood City, CA) the investigators performed the randomisation. Patients in the SAP group received a Paradigm REAL-Time System (Medtronic MiniMed, Inc., Northridge, CA), comprising a needle type subcutaneous continuous glucose sensor with an insulin pump delivering short-acting insulin analogues. A signal is generated by a glucose-oxidase reaction in the sensor and is sent wirelessly to a monitor via radio frequency. Glucose values are displayed on a
A pager-sized insulin pump device. For initiation the monitor requires calibrations at 2 and before 6 hours and hereafter two calibrations per 24 hours. A glucose value is displayed every 5 minutes. The system is equipped with an alarm function for upcoming hypo- and hyperglycaemia. When responding to an alarm, patients were instructed to verify the glucose displayed by the sensor with a SMBG and make treatment decisions based on the SMBG value. Alarm settings were initially set and adjusted at discretion of both the patient and treating study staff. Furthermore, a Bolus Wizard® program provided mealtime insulin dosing advice to the patient, taking into account current glucose value (based on sensor data or SMBG values), estimated amount of active insulin, amount of carbohydrates in the upcoming meal, individual insulin sensitivity, carbohydrate sensitivity, and glucose target values. Thus, this device provides the patient with a combination of continuous glucose data stream with the optimal way to deliver insulin, enabling optimal self-management. Patients were trained to use the device within two weeks after randomisation and to change both the insulin catheter and glucose sensor every three days. At 13- and 26 weeks patients visited the investigating centre and data from the sensor was downloaded and if necessary therapy adjustments were made based on the downloaded data. No specific instructions with regard to insulin dosing or other device specific adjustments were provided to the patients other than during the training phase and 13- and 26 week visit.

The patients in the MDI group received standard care, which included MDI therapy with rapid-acting insulin analogue before meals and long-acting analogues or human insulin. The advised SMBG frequency was at least 3 times per day. The MDI patients received a blinded 6-day CGM measurement before the 13- and 26 week visits, using the Guardian® REAL-Time Clinical. No treatment advice was provided based on the CGM measurements at these time points. They did receive regular treatment- and dose adjustment advice as usual. In the second part of the trial (between 13- and 26 weeks) patients in the SAP and MDI group were to receive the same amount of study staff attention. Carbohydrate counting was strongly encouraged in all participants, but not compulsory. For both groups blood was drawn at baseline, 13-, and 26 weeks and stored at -80 C for HbA1c determination in the central lab in the Netherlands after the trial. All samples were determined in one-run using the High Performance Liquid Chromatography method (Tosoh-G8, Tosoh, Japan, DCCT aligned). The data from the devices was downloaded at baseline, 13-, and 26-weeks via a web-based application in the investigating centre, using Carelink® Clinical (Medtronic MiniMed, Inc., Northridge, CA). The Carelink® system was not yet available for
outpatient use at start of our trial. The contact time with the study personnel was registered. The occurrence of severe hypoglycaemia (clinical episode of hypoglycaemia ≤2.8 mmol/l, resulting in seizure or coma, intravenous glucose or glucagon, or any 3rd party assistance) and ketoacidosis were considered adverse events. Finally, serious adverse events (SAE) and their possible relation to the study and/or device were listed.

**Outcome Measures**

The primary outcome was difference in HbA1c between baseline and 26 weeks. Also we calculated the change between 13 and 26 weeks. The sensor data were analyzed for minutes in hyperglycaemia >11.1 mmol/l and hypoglycaemia <4.0 mmol/l expressed as the percentage of the total monitoring time. Also the number of hyper- and hypoglycaemia events per day were calculated. For both groups a time-window of up to six-days prior to downloading of the available data was used to determine
the sensor derived endpoints. Sensor use was calculated for the SAP group as the average hours/week sensor use and percentage of sensor use during the whole trial. Furthermore, the proportion of patients reaching HbA1c <7%, the contact time with the study personnel, the number of SMBG measurements per three weeks and total daily insulin dose per patient were calculated.

**Patient Reported Outcomes (PRO)**

Questionnaires were administered at baseline and end of trial. Health-related quality of life was assessed using the SF-36 version 2 (SF-36v2)\(^1\)\(^5\), which comprises eight subscales: Physical Functioning (PF), Role-Physical (RP), Bodily Pain (BP), General Health (GH), Vitality (VT), Social Functioning (SF), Role-Emotional (RE), and Mental Health (MH). Scores were transformed to a 0 to 100 (highest health score) scale. The Problem Areas in Diabetes Scale (PAID) is a 20 item questionnaire that scores diabetes related physiological distress.\(^1\)\(^6\) Scores were transformed to a 0-100 scale, with higher scores indicating more problems. The Diabetes Treatment Satisfaction Questionnaire (DTSQ) comprises six items and is scored on a 0-36 scale, with higher scores indicating higher satisfaction. Two additional items concern perceived frequency of hypo- and hyperglycaemia, scored on a 0 (lowest frequency) to 6 (highest frequency) scale.\(^1\)\(^7\) Finally, the 13-item worry-subscale of the Hypoglycaemia Fear Survey (HFS) was administered.\(^1\)\(^8\) The HFS scores were transformed to a 0-100 scale, higher scores indicating more hypoglycaemia related fear. The HFS and PAID could not be administered in all centres, due to lack of validated translations.

**Statistical Methods**

Assuming a standard deviation of 1.3% in HbA1c, a two-sided t-test with an alpha level of 0.05, sample size calculations indicated that 36 patients per group would be needed to detect a between-group difference of 1.0% in HbA1c with 90% power. A drop-out rate of 30% was anticipated, and the original goal was to randomise 52 patients per group. As the drop-out rate was much lower than expected, we stopped inclusion after having randomised 83 patients.

All analyses were predefined but the percentage of participants reaching the <7% target and analysis on sensor use. Analyses were based on the intention to treat principle. The primary outcome measure, change in HbA1c between baseline and 26 weeks, was analyzed using an ANCOVA model with treatment and centre as fixed effects and the baseline HbA1c value as covariate. If a patient dropped out after 13 weeks, the last observation was carried forward (LOCF) to 26 weeks. HbA1c after 13
weeks, the sensor-derived endpoints and questionnaire scores were analysed using the ANCOVA model as defined above and are reported as mean with standard deviation (SD). The difference in change in HbA1c between 13 and 26 weeks was analysed using repeated measurements ANOVA with centre and treatment as fixed effects and baseline HbA1c, time and the interaction between treatment as covariates and subject as random factor. Hours of sensor use/week in the SAP group during the trial were related to change in HbA1c after 26 weeks and corrected for baseline HbA1c. Differences in contact time were reported as median with IQR and compared using the Mann-Whitney $U$ test. The differences in proportions of patients reaching HbA1c <7% and experiencing a severe hypoglycaemic episode were calculated using the chi-square test.

RESULTS

Patients
The participant flow is displayed in Figure 2. After screening ninety-three patients, eighty-seven started the trial. Before randomisation, 4 patients dropped-out after the baseline sensor measurement, all indicating that they did not tolerate the sensor. Eighty-three patients were randomised. Baseline characteristics of the two groups were comparable as displayed in Table 1. In the SAP group 43/44 (98%) patients completed the trial and 35/39 (90%) in the MDI group. The patient dropping out in the SAP group did not tolerate the intensity of the SAP treatment. In the MDI group one patient stopped for unknown reasons, one patient due to surgery for aorta bifurcation prosthesis, one patient because of dissatisfaction about the randomisation outcome, and one patient was lost to follow up. Three baseline HbA1c blood samples got lost. HbA1c analyses could be performed on 41/44 patients from the SAP group (1 drop-out, 2 missing baseline samples) and 36/39 patients from the MDI group (4 drop out, with 2 LOCF, one missing baseline sample). After 26 weeks, the total daily insulin dose in the SAP group decreased to 46.7 (SD 16.5) units and somewhat increased in the MDI group to 57.8 (SD 18.1) units per day, with a baseline and centre adjusted difference in change between the groups of -11.0 units per day (95% confidence interval -16.1 to -5.9, $p<0.001$). Prior to the study patients in the SAP group used 76 (SD 40) SMBG per three weeks, which increased to 87 (SD 43) at the end of the trial. For patients in the MDI group, the number of SMBGs per three weeks increased from 70 (SD 38) to 82 (SD 48). This was a non-significant difference in change, $p=0.38.$
Sensor augmented pump therapy in suboptimally controlled DM type 1

Figure 2- participant flow, horizontal arrows indicating reasons for dropping out

Table 1- baseline characteristics

<table>
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<tr>
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<th>SAP (n=44)</th>
<th>MDI (n=39)</th>
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</thead>
<tbody>
<tr>
<td>Age, years (mean, (SD))</td>
<td>39.3 (11.9)</td>
<td>37.3 (10.7)</td>
</tr>
<tr>
<td>Female sex (n, (%))</td>
<td>22 (50.0)</td>
<td>18 (46.2)</td>
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<tr>
<td>Diabetes duration, years (mean (SD))</td>
<td>16.9 (10.7)</td>
<td>21.0 (9.4)</td>
</tr>
<tr>
<td>HbA1c baseline, % (mean (SD))</td>
<td>8.47 (0.94)</td>
<td>8.64 (0.86)</td>
</tr>
<tr>
<td>Total daily insulin dose, units (mean (SD))</td>
<td>54.5 (21.0)</td>
<td>53.9 (14.0)</td>
</tr>
<tr>
<td>Patients experiencing severe hypoglycaemia the last 12 months before randomisation (n, (%))</td>
<td>6 (13.6)</td>
<td>3 (7.7)</td>
</tr>
<tr>
<td>Country (n, (%))</td>
<td></td>
<td></td>
</tr>
<tr>
<td>-Denmark</td>
<td>13 (29.5)</td>
<td>11 (28.2)</td>
</tr>
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<td>2 (5.1)</td>
</tr>
<tr>
<td>-The Netherlands</td>
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</tr>
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<td>-Sweden</td>
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<td>-United Kingdom</td>
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</tr>
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</tr>
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<td>-Italy</td>
<td>6 (13.6)</td>
<td>6 (15.4)</td>
</tr>
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</table>

Abbreviations: SAP=Sensor Augmented Pump group, MDI=Multiple Daily Injections group, CGM= Continuous Glucose Monitoring, HbA1c=Haemoglobin A1c
Glycaemic Control

The least square mean (LS mean) from the ANCOVA model for treatment effect, adjusted for baseline HbA1c and centre was -1.21% (95% confidence interval -1.52 to -0.90, \( p<0.001 \)). The crude mean difference in change in HbA1c after 26 weeks was -1.10% (95% confidence interval -1.47 to -0.73, \( p<0.001 \)) in favour of the SAP group (Figure 3 and Table 2). The LS mean difference in change in HbA1c after 13 weeks was -1.22% (95% confidence interval -1.59 to -0.86, \( p<0.001 \)). No significant difference in change was observed between 13 and 26 weeks, \( p=0.85 \). The proportion of patients reaching EASD/ADA HbA1c target of <7% was 34% in the SAP group and 0% in the MDI group, \( p<0.001 \). The LS mean difference in change in percentage of sensor-time spent in hyperglycaemia after 26 weeks was -17.3% (95% confidence interval -25.1 to -9.5, \( p<0.001 \)). No significant difference in change in percentage of time spent in hypoglycaemia after 26 weeks was found between groups: 0.0% (95% confidence interval -1.6 to 1.7, \( p=0.96 \)). The change in number of hyper- or hypoglycaemic events did not differ between the groups. Sensor derived endpoints are summarised in Table 3.

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*The baseline and treating centre adjusted HbA1c change (ANCOVA-model) was: -1.21% (95% CI -1.52 to -0.90, \( p<0.001 \))

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**Figure 3-** haemoglobin A1c (HbA1c) results

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<table>
<thead>
<tr>
<th></th>
<th>SAP (n=41)</th>
<th>MDI (n=36)</th>
<th>Difference (95% CI)</th>
<th>p value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>8.46 (0.95)</td>
<td>8.59 (0.82)</td>
<td>0.13 (N/A)</td>
<td></td>
</tr>
<tr>
<td>13 weeks</td>
<td>7.29 (0.71)</td>
<td>8.55 (1.21)</td>
<td>1.25 (0.79 to 1.72)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Baseline-13 weeks</td>
<td>-1.17 (0.93)</td>
<td>-0.05 (0.73)</td>
<td>-1.13 (-1.51 to -0.74)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LSM</td>
<td>-1.22 (-1.59 to -0.86)</td>
<td>&lt;0.001</td>
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<td></td>
</tr>
<tr>
<td>26 weeks</td>
<td>7.23 (0.65)</td>
<td>8.46 (1.04)</td>
<td>1.23 (0.83 to 1.63)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Baseline-26 weeks</td>
<td>-1.23 (1.01)</td>
<td>-0.13 (0.56)</td>
<td>-1.10 (-1.47 to -0.73)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LSM</td>
<td>-1.21 (-1.52 to -0.90)</td>
<td>&lt;0.001</td>
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</tr>
<tr>
<td>13-26 weeks</td>
<td>-0.06 (0.57)</td>
<td>-0.09 (0.51)</td>
<td>-0.03 (-0.27 to 0.21)</td>
<td>0.83</td>
</tr>
<tr>
<td>LSM</td>
<td>-0.02 (-0.27 to 0.21)</td>
<td>0.85</td>
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</tbody>
</table>

Abbreviations: HbA1c = haemoglobin A1c, SAP = Sensor Augmented Pump group, MDI = Multiple Daily Injections group, N/A = not applicable, LSM = least square mean.

* p value for comparison between the SAP and MDI group
† Difference in HbA1c change in HbA1c between the SAP and MDI group after 13 and 26 weeks. LSM from the ANCOVA model, adjusted for Investigating Centre and baseline HbA1c.
‡ Difference in change in HbA1c between the SAP and MDI Group between 13 weeks and 26 weeks from repeated measurements ANOVA, adjusted for centre, baseline HbA1c, the factor time and the interaction between treatment and time. Patient identification number was included as random factor.
**Table 3: sensor data**

<table>
<thead>
<tr>
<th></th>
<th>SAP (n=40) mean (SD)</th>
<th>MDI (n=31) mean (SD)</th>
<th>Difference (95 % CI)</th>
<th>p value*</th>
</tr>
</thead>
<tbody>
<tr>
<td>% of time in hyperglycaemia</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>38.0 (17.4)</td>
<td>40.1 (18.4)</td>
<td>2.1 (N/A)</td>
<td></td>
</tr>
<tr>
<td>26 weeks</td>
<td>21.6 (12.2)</td>
<td>38.2 (21.5)</td>
<td>16.5 (7.8 to 25.2)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LSM Δ Baseline-26 weeks†</td>
<td></td>
<td></td>
<td>-17.3 (-25.1 to -9.5)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>% of time in hypoglycaemia</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>3.9 (4.7)</td>
<td>2.5 (2.8)</td>
<td>1.4 (N/A)</td>
<td></td>
</tr>
<tr>
<td>26 weeks</td>
<td>2.7 (3.4)</td>
<td>2.5 (3.6)</td>
<td>0.2 (-1.4 to 1.9)</td>
<td>0.79</td>
</tr>
<tr>
<td>LSM Δ Baseline-26 weeks†</td>
<td></td>
<td></td>
<td>0.0 (-1.6 to 1.7)</td>
<td>0.96</td>
</tr>
<tr>
<td>Number of hyperglycaemic events‡</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>2.4 (0.6)</td>
<td>2.5 (0.6)</td>
<td>0.2 (N/A)</td>
<td></td>
</tr>
<tr>
<td>26 weeks</td>
<td>2.1 (0.8)</td>
<td>2.2 (0.7)</td>
<td>0.2 (-0.2 to 0.5)</td>
<td>0.30</td>
</tr>
<tr>
<td>LSM Δ Baseline-26 weeks†</td>
<td></td>
<td></td>
<td>-0.2 (-0.6 to 0.1)</td>
<td>0.21</td>
</tr>
<tr>
<td>Number of hypoglycaemic events‡</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>0.7 (0.1)</td>
<td>0.5 (0.5)</td>
<td>0.2 (N/A)</td>
<td></td>
</tr>
<tr>
<td>26 weeks</td>
<td>0.7 (0.7)</td>
<td>0.6 (0.7)</td>
<td>0.1 (-0.2 to 0.5)</td>
<td>0.40</td>
</tr>
<tr>
<td>LSM Δ Baseline-26 weeks†</td>
<td></td>
<td></td>
<td>-0.1 (-0.5 to 0.2)</td>
<td>0.50</td>
</tr>
</tbody>
</table>

Abbreviations: HbA₁c= haemoglobin A₁c, SAP=Sensor Augmented Pump group, MDI=Multiple Daily Injections group, N/A= not applicable, LSM= least square mean, CI=confidence interval

Hyperglycaemia >11.1 mmol/l, Hypoglycaemia <4.0 mmol/l

*p value for comparison between the SAP and MDI group

†Difference in change between the SAP and MDI group after 26 weeks; LSM from the ANCOVA model, adjusted for investigating centre and baseline values

‡Number of events, standardised per day. An event was counted when the sensor glucose value crossed the hyper- or hypoglycaemia threshold, followed by a 30 minute period between 4.0 mmol/l and 11.1 mmol/l
Patient Reported Outcomes
The patient reported outcomes are shown in Table 4. The difference in change in the PAID score was significant -7.9 (95% confidence interval -15.1 to -0.61, \( p=0.03 \)) in favour of the SAP group. Also the DTSQs and DTSQ “perceived frequency of hyperglycaemia” scores improved significantly more in SAP group as compared to the MDI group. For the SF-36v2 questionnaire, only the change in the General Health and Social Functioning subscales differed significantly, both in favour of the SAP group.

Contact Time and Sensor Usage
The median total contact time during the trial was 240 minutes (IQR 195 to 353) in the MDI group and 690 minutes (526 to 1028) in the SAP group (\( p<0.001 \)). The median contact time in the SAP and MDI group before week 13 was 553 minutes (423-825) and 135 minutes (108 to 218) respectively (\( p=0.001 \)). Between week 13 and the end of the trial this was 75 minutes (60 to 120) in the SAP group and 60 minutes (40 to 75) in the MDI group (\( p=0.001 \)).

The mean sensor use in the SAP group was 4.5 (SD 1.0) days/per week over the whole trial period and 79% of the patients using the sensor more than 60% of the time. The Bolus Wizard® was used by 86% of the SAP group patients at the end of the trial. There was no evident relation between sensor use and HbA1c decrease within the SAP group, when adjusted for baseline HbA1c, with a regression coefficient of 0.006, \( p=0.20 \). Furthermore, when examining contact time, sensor use, age, sex and baseline HbA1c as predictors for HbA1c decrease after 26 weeks in a multivariate linear regression model, only baseline HbA1c was a significant predictor (\( \beta= -0.80, 95\% \text{ CI } -1.06 \text{ to } -0.53, \ p<0.001 \)).
Table 4 - patient reported outcomes

<table>
<thead>
<tr>
<th></th>
<th>SAP mean (SD)</th>
<th>MDI mean (SD)</th>
<th>Difference (95 % CI)</th>
<th>p value*</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Problem Areas In Diabetes scale</strong></td>
<td>N=30</td>
<td>N=24</td>
<td></td>
<td></td>
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<tr>
<td>Baseline</td>
<td>32.4 (18.8)</td>
<td>26.5 (18.4)</td>
<td>5.8 (N/A)</td>
<td></td>
</tr>
<tr>
<td>26 weeks</td>
<td>21.0 (19.3)</td>
<td>23.7 (19.4)</td>
<td>2.7 (-7.9 to 13.4)</td>
<td>0.61</td>
</tr>
<tr>
<td>LSM Δ Baseline-26 weeks†</td>
<td></td>
<td></td>
<td>-7.9 (-15.1 to -0.61)</td>
<td>0.03</td>
</tr>
<tr>
<td><strong>Hypoglycaemia Fear Survey</strong></td>
<td>N=35</td>
<td>N=28</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>29.8 (19.2)</td>
<td>21.0 (17.7)</td>
<td>8.8 (N/A)</td>
<td></td>
</tr>
<tr>
<td>26 weeks</td>
<td>24.1 (20.2)</td>
<td>20.3 (16.9)</td>
<td>3.9 (-5.7 to 13.4)</td>
<td>0.42</td>
</tr>
<tr>
<td>LSM Δ Baseline-26 weeks†</td>
<td></td>
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<td>-3.2 (-10.0 to 3.7)</td>
<td>0.36</td>
</tr>
<tr>
<td><strong>Diabetes Treatment Satisfaction Questionnaire</strong></td>
<td>N=41</td>
<td>N=35</td>
<td></td>
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<tr>
<td>Baseline</td>
<td>21.6 (5.5)</td>
<td>22.5 (6.3)</td>
<td>1.0 (N/A)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>26 weeks</td>
<td>32.4 (3.5)</td>
<td>23.8 (6.2)</td>
<td>8.6 (6.2 to 11.0)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>LSM Δ Baseline-26 weeks†</td>
<td></td>
<td></td>
<td>9.3 (7.3 to 11.3)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Perceived frequency of hyperglycaemia</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>4.4 (1.2)</td>
<td>4.3 (1.3)</td>
<td>0.1 (N/A)</td>
<td></td>
</tr>
<tr>
<td>26 weeks</td>
<td>2.4 (1.2)</td>
<td>3.9 (1.2)</td>
<td>1.5 (1.0 to 2.1)</td>
<td>&lt;0.001</td>
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<tr>
<td>LSM Δ Baseline-26 weeks†</td>
<td></td>
<td></td>
<td>-1.6 (-2.1 to -1.1)</td>
<td>&lt;0.001</td>
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<tr>
<td><strong>Perceived frequency of hypoglycaemia</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Baseline</td>
<td>2.3 (1.3)</td>
<td>2.3 (1.4)</td>
<td>0.1</td>
<td></td>
</tr>
<tr>
<td>26 weeks</td>
<td>2.4 (1.2)</td>
<td>2.2 (1.3)</td>
<td>0.2 (-0.4 to 0.8)</td>
<td>0.51</td>
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<tr>
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<td>-0.3 (-0.8 to 0.3)</td>
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<tr>
<td><strong>SF-36</strong></td>
<td>N=42</td>
<td>N=33</td>
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<tr>
<td>Baseline</td>
<td>89.4 (14.5)</td>
<td>90.5 (14.3)</td>
<td>1.0 (N/A)</td>
<td></td>
</tr>
<tr>
<td>Physical Functioning</td>
<td>76.8 (23.8)</td>
<td>84.4 (19.3)</td>
<td>7.6 (N/A)</td>
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<tr>
<td>Bodily Pain</td>
<td>78.9 (25.4)</td>
<td>78.7 (23.0)</td>
<td>0.2 (N/A)</td>
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</tr>
<tr>
<td>General Health</td>
<td>55.5 (20.3)</td>
<td>59.8 (22.3)</td>
<td>4.3 (N/A)</td>
<td></td>
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<tr>
<td>Vitality</td>
<td>53.9 (20.0)</td>
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<td>7.1 (N/A)</td>
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<tr>
<td>Social Functioning</td>
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<td>86.4 (21.0)</td>
<td>4.8 (N/A)</td>
<td></td>
</tr>
<tr>
<td>Role-Emotional</td>
<td>84.9 (20.4)</td>
<td>89.6 (16.7)</td>
<td>4.4 (N/A)</td>
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</tr>
<tr>
<td>Mental Health</td>
<td>72.6 (14.8)</td>
<td>77.9 (20.2)</td>
<td>5.3 (N/A)</td>
<td></td>
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<tr>
<td><strong>26 weeks</strong></td>
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</tr>
<tr>
<td>Physical Functioning</td>
<td>92.7 (11.2)</td>
<td>91.4 (12.7)</td>
<td>1.4 (-4.1 to 6.9)</td>
<td>0.62</td>
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<tr>
<td>Bodily Pain</td>
<td>85.7 (20.7)</td>
<td>87.3 (20.4)</td>
<td>1.6 (-11.2 to 8.0)</td>
<td>0.74</td>
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<tr>
<td>General Health</td>
<td>79.9 (24.4)</td>
<td>78.7 (22.6)</td>
<td>1.3 (-9.7 to 12.2)</td>
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<tr>
<td>Vitality</td>
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<td>63.1 (19.1)</td>
<td>4.5 (-5.0 to 14.1)</td>
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<tr>
<td>Social Functioning</td>
<td>66.7 (20.2)</td>
<td>65.2 (19.3)</td>
<td>1.5 (-7.7 to 10.7)</td>
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</tr>
<tr>
<td>Role-Emotional</td>
<td>89.3 (16.0)</td>
<td>82.2 (25.2)</td>
<td>7.1 (-3.0 to 17.2)</td>
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<tr>
<td>Mental Health</td>
<td>87.1 (19.6)</td>
<td>88.0 (16.0)</td>
<td>0.9 (-7.6 to 9.4)</td>
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</tr>
<tr>
<td><strong>LSM Δ Baseline-26 weeks†</strong></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Physical Functioning</td>
<td>2.2 (-0.7 to 5.1)</td>
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<td>0.13</td>
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</tr>
<tr>
<td>Bodily Pain</td>
<td>2.1 (-6.1 to 10.3)</td>
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<td>0.62</td>
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</tr>
<tr>
<td>General Health</td>
<td>1.7 (-7.6 to 11.0)</td>
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<td>0.71</td>
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</tr>
<tr>
<td>Vitality</td>
<td>7.9 (0.5 to 15.3)</td>
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<td>0.04</td>
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<td>Social Functioning</td>
<td>6.4 (-1.2 to 14.1)</td>
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<td>0.10</td>
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<tr>
<td>Role-Emotional</td>
<td>9.8 (1.3 to 18.3)</td>
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<td>Mental Health</td>
<td>4.8 (-1.6 to 11.1)</td>
<td></td>
<td>0.14</td>
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</table>
Hypoglycaemia and Adverse Events
There was a non-significant difference in the occurrence of severe hypoglycaemia, with 4 episodes in the SAP group (9%) and 1 episode in the MDI group (3%), p=0.21. This is 19 episodes /100 person years in the SAP group and 6/100 person years in the MDI group. All patients in the SAP group were wearing the device during the severe hypoglycaemia. In total, 7 SAE’s were reported, of which 2 occurred in the SAP group and 5 in the MDI group. Only one SAE was reported as being related to the device in the SAP group, where the patient was admitted to the hospital for ketoacidosis because of pump-failure. Other SAEs were: surgery for aorta bifurcation prosthesis, hemianopsia, respiratory tract infection, and ketoacidosis (x2) in the MDI group and acute gastritis in the SAP group. Twenty patients reported 26 probable or possible device related adverse events. Of these, 17 patients reported skin related problems (itch/exanthema/infection/redness/plaster allergy/bruising/hematoma) at the sensor or insulin infusion site.

DISCUSSION

Sensor augmented pump therapy (SAP) significantly lowered HbA₁c after 26 weeks by -1.21% as compared to multiple daily injection therapy (MDI) without a significant increase in hypoglycaemia. SAP therapy was associated with an improvement in treatment satisfaction and diabetes related distress. These results were observed in patients failing on optimal MDI and SMBG therapy in specialized CSII centres.

This is the first trial with adequate duration and sample size comparing SAP to MDI therapy in type 1 diabetes patients with suboptimal control. We thought it to be appropriate to compare SAP therapy to MDI, as the number of patients using insulin pump therapy in stead of MDI is relatively small⁵ Therefore, MDI reflects the current standard of care. Furthermore, previous trials have already investigated the addition of CGM to MDI or pump therapy and the initiation of
SAP therapy vs. the initiation of insulin pump therapy.\textsuperscript{11;19;20} The efficacy of CSII therapy with short-acting analogues alone is about \(-0.3\%\) as compared to MDI therapy.\textsuperscript{10} This is however highly dependent on baseline HbA\textsubscript{1c}\textsuperscript{10}. The JDRF trial demonstrated the efficacy of sensor use as compared to MDI therapy in adult type 1 diabetes patients, lowering HbA\textsubscript{1c} by \(-0.5\%\) from 7.6\% at baseline.\textsuperscript{11} Other trials investigating the efficacy of sensor use in poorly regulated type 1 diabetes patients have found effects on HbA1c decrease ranging from 0 to \(-0.6\%\).\textsuperscript{21} Thus, the magnitude of change of \(-1.21\%\) in the Eurythmics trial seems at least a summation of the effects of CSII and CGM therapy. This supports the notion that integration of CSII and CGM provides a new treatment platform. This is further substantiated by the use of the mealtime insulin dose advisor by 86\% of the SAP group, establishing active communication between the insulin pump, CGM and the patient.

A limitation of the study was the by necessity unblinded character. Moreover, the patients in the SAP group received more attention from the study staff especially in the first part of the trial, because of the device specific training phase. This difference in attention, to the best of our knowledge now quantified for the first time in a diabetes device trial, may contribute to HbA\textsubscript{1c} lowering.\textsuperscript{20;22} We believe however that a temporary increase in time spent with the patient reflects the real-life situation and can not be set apart when starting SAP therapy in patients using MDI. Furthermore, in multivariate analysis, the duration of contact time was not a significant predictor of HbA\textsubscript{1c} decrease and the HbA\textsubscript{1c} lowering reached in the first part of the trial in the SAP group was sustained between 13 and 26 weeks, when the difference in attention given to both study groups was only 15 minutes. Notably, in the MDI group there was a minimal HbA\textsubscript{1c} decrease and no study effect was observed. Perhaps this is not so surprising when considering that all other attempts to optimise their MDI/SMBG treatment failed, and the limited additional attention given to these patients.

Prior to randomisation, 4 patients dropped out because they did not tolerate the CGM device, but hereafter only 1 patient randomised to SAP did not complete the trial. In the JDRF trial, patients had to complete a run-in phase before they could be randomised.\textsuperscript{11} Thus in both trials the efficacy of sensor or SAP therapy was investigated in patients with type 1 diabetes, who proved to be tolerating the device.

The rate of severe hypoglycaemia at 26 weeks was low in both groups, with a non-significantly higher rate in the SAP group (9\% vs. 3\%, \(p=0.21\)), that seemed to be more susceptible to severe hypoglycaemia at baseline as compared to the MDI group. Thus, with a more pronounced HbA\textsubscript{1c} lowering, the severe hypoglycaemia
frequencies are similar to those found in the JDRF CGM trial and much lower than observed in the DCCT.\textsuperscript{1,11} The apparent lack of decrease in hypoglycaemia in the SAP group can have several explanations. First, due to the decline of cognitive functions during hypoglycaemia patients are less adequate in responding to acoustic or vibration alarms.\textsuperscript{23} Also the CGM device is more likely to be put aside during high risk activities such as intensive sports. Finally, the sensor inaccuracy can contribute to missing episodes of hypoglycaemia. We did not specifically assess sensor performance in this trial. The accuracy of glucose sensors has however been investigated extensively and is known to be deteriorating in the hypoglycaemic range.\textsuperscript{7}

The analyses of the sensor derived data also show that a significant decrease in hyperglycaemia AUC in the SAP group as compared to the MDI group is not accompanied by an increase in time spent in hypoglycaemia. Also the number of hypoglycaemic events did not differ between both groups. What did change was the percentage of time spent in hyperglycaemia, which was significantly lower in the SAP group after 26 weeks. The number of hyperglycaemic events did not differ significantly between the SAP and MDI group, suggesting that the beneficial effect of the SAP treatment results from reducing the duration (and not the number) of hyperglycaemic events as they occur.

We found an improvement in change in PRO scores concerning diabetes related distress, perceived frequency of hyperglycaemia, general health, social functioning, and treatment satisfaction. Furthermore, the use of SAP therapy was not accompanied by an increase the fear- or perceived frequency of hypoglycaemia. These PRO outcomes do not confirm historical fears of data overload due to CGM. Sensor use in the trial was on average 4.5 days/week and most patients used the sensor >60% of the time. In contrast with previous CGM trials, we could not find a relation between CGM use and change in HbA\textsubscript{1c}.\textsuperscript{11,19,20} This trial was however not designed to investigate this relationship. It is noteworthy that the substantial improvement in glycaemic control with frequent sensor use was seen in a patient group not easy to reach, under treatment in experienced pump centres and failing on optimised MDI/SMBG therapy.

In conclusion, these study results show that, as compared to MDI treatment, SAP treatment in motivated but suboptimally controlled type 1 diabetes patients results in a considerable HbA\textsubscript{1c} reduction and improvement in quality of life, without increasing hypoglycaemia. The magnitude of the difference in change in HbA1c of -1.21% may be due to the combined effect of pump, sensor, Bolus Wizard\textsuperscript{®} and the process of starting SAP therapy in this hard to reach population.
Acknowledgements
This trial was financially supported by Medtronic International Trading Sàrl. This was an investigator-initiated trial. The funding source had an advising role in trial design details and drafting of the report and was only involved in the collection of the sensor data. The funding source had no role in the conduct of the analyses, interpretation of the data or in the decision to approve publication. Chantal Mathieu is a clinical researcher of the FWO (Fund for Research Flanders). We further acknowledge the following people involved in the execution of the trial: Hilde Morobé, Peggy Callewaert, Marijke Carpentier, Conny Peeters, Kate Green, Dr. Danijela Tatovic, Dr. Silvana Costa, Dr. Andrea Egger, Dr. Andrea Lanker, Peggy Wentzel, Dorien Dragt, Dr. C.B. Brouwer, Merete Meldgaard, Ingrid Wetterholtz, and Hanna Söderling.
REFERENCES


Sensor augmented insulin pump therapy to treat hyperglycaemia at the coronary care unit; a randomised controlled pilot trial

J Hermanides, AE Engström, IME Wentholt, KD Sjauw, JBL Hoekstra, JPS Henriques, JH DeVries

Diabetes Technology & Therapeutics, In Press
ABSTRACT

Background The relationship between admission hyperglycaemia and adverse outcome in myocardial infarction has been shown consistently. However, achieving and maintaining normoglycaemia in STEMI-patients has proven difficult. This study aimed to investigate the efficacy of sensor augmented insulin pump therapy (SAP) to treat hyperglycaemia.

Methods In a randomised controlled pilot trial, we assigned 20 patients, aged 30-80 years, admitted with STEMI and hyperglycaemia (>=7.8 mmol/l) to receive either 48 hours of strict glycaemic control with an subcutaneous insulin pump augmented with a continuous glucose monitor (SAP group) or to treatment according to standard practice (Control group) with glucose measured by blinded CGM. The main outcome measure proportion of time spent in hyperglycaemia.

Results The median treatment time was 47.0 hours (IQR 46.2 to 48.0) in the SAP group and 44.6 (IQR 22.0 to 48.6) in the Control group. The median proportion of time >=7.8 mmol/l was 14.6% (IQR 10.5 to 18.5) in the SAP group and 36.3% in the control group (IQR 26.0 to 80.4), p=0.006. The proportion of time <=3.9 mmol/l was 8.9% (IQR 8.3 to 12.5) in the SAP group vs. 0% (IQR 0 to 2) in the Control group, p<0.001. Plasma glucose decreased significantly in SAP group as compared to the Control group, p=0.025.

Conclusions SAP therapy is effective in reducing hyperglycaemia in STEMI patients on the coronary care unit. This is accompanied by a small but significant increase in hypoglycaemia. Although a promising tool for in-hospital hyperglycaemia therapy, SAP needs improvement before continuing to large scale randomised controlled trials.
INTRODUCTION

In patients admitted for acute myocardial infarction (AMI), elevated admission glucose levels are strongly predictive of heart failure, shock and mortality. 1-4 In the first randomised controlled study to treat Diabetic Patients with Acute Myocardial Infarction (DIGAMI), intensive glucose lowering therapy significantly reduced both short- and long term mortality. 5,6 Two following trials aiming to treat hyperglycaemia in patients with- and without diabetes mellitus and AMI (DIGAMI 2 and HI-5) could not reproduce earlier results.7,8 The authors attributed this to disappointing recruitment rates, but also to the lack of significant difference in glucose control achieved between the intervention and control groups. Indeed, post-hoc analyses showed that hyperglycaemia remained an important predictor of mortality.7,8 Recently, Kosiborod and colleagues showed that glucose normalisation after AMI is associated with improved survival. 9 It thus seems important but difficult to lower glucose in the coronary care setting. An important barrier to implementation of intensive glucose control in the coronary care unit may be the fear for hypoglycaemia that invariably accompanies glucose lowering therapy.10,11 Furthermore, it has proven hard to handle postprandial glucose excursions in hospitalised patients who resume normal eating.12 The use of insulin pumps augmented with a continuous subcutaneous glucose monitor (CGM) could improve glucose lowering therapy in the coronary care unit (CCU). Using the continuous stream of glucose data with preset alarms for hypo- and hyperglycaemia, the subcutaneous insulin infusion rates can be adjusted to maintain euglycaemia. Furthermore, a mealbolus advisor can be used to limit postprandial hyperglycaemia.13 The system has already proven beneficial in treating patients with type 1 diabetes in outpatient settings.14-16 In this study, we investigated the efficacy of sensor augmented pump therapy to treat hyperglycaemia in patients admitted to the CCU for AMI.

METHODS

Design and patients
We performed a randomised controlled pilot trial, including patients admitted to the CCU of the Academic Medical Centre (Amsterdam, The Netherlands), a university hospital. Patients with an admission glucose of >=7.8 mmol/l (measured from a venous blood sample using the Accu-Check Inform®, Roche Diagnostics, Basel Switzerland), aged 30-80 years, and ST-elevation myocardial infarction
(STEMI), treated by primary percutaneous coronary intervention (PCI), were included. Exclusion criteria were known diabetes mellitus type 1, abdominal abnormalities that might hinder either glucose measurement by the sensor or the continuous subcutaneous insulin infusion and simultaneous participation in other studies. The study was approved by the ethic committee of the Academic Medical Centre and performed in accordance with the declaration of Helsinki. All patients provided written informed consent. The study is registered with controlled-trials.com, ISRCTN55085730.

**Procedures**

After inclusion, patients were randomised to either 48 hours of glucose control with sensor augmented pump therapy (SAP group) or blinded continuous monitoring only with treatment according to standard practice (Control group). A flow chart is provided in Figure 1.

![Figure 1: Study flow-chart, SAP=Sensor Augmented Pump, CGM=Continuous subcutaneous Glucose Monitor](image)

In the SAP group, preceding PCI, an intravenous starting insulin bolus was injected based on the admission glucose, using an adapted standardised algorithm *(Appendix 1)* from Bode et al and adjusted by Nobels et al. The Paradigm® Real-Time system (Medtronic MiniMed, Inc., Northridge, CA), combines a continuous glucose sensor and insulin pump. Both need insertion subcutaneously in the abdominal periumbilical area at different sites. Two hours after insertion and
initiation (inherent to the system), the system could be calibrated and the CGM and insulin pump were started. The CGM provides a glucose value every 5 minutes. The alarm thresholds were set at 4.7 mmol/l for hypo- and 6.1 mmol/l for hyperglycaemia. Because the frequency of the alarms requesting a blood glucose check and recalibration was too time consuming for the nursing personnel we changed the upper alarm threshold to 7.1 mmol/l after the first 5 patients in the SAP group. On request of the nursing staff, the lower alarm threshold was set at 4.4 mmol/l and the upper at 7.5 mmol/l for the last two patients.

The nursing staff was instructed to adjust the basal insulin rates responding to alarms according to the algorithm (Appendix I). Using the BolusWizard® the study staff calculated the mealtime insulin bolus. The BolusWizard® program provides a mealtime insulin bolus advice taking into account the current glucose value, insulin administration rate, patient specific insulin/carbohydrate sensitivity and the amount of carbohydrates to be ingested. The insulin/carbohydrate sensitivity was based on the total daily insulin need of the patient, which was calculated from the amount of insulin needed to achieve normoglycaemia in each particular patient.

In the control group the CGM of the Paradigm® Real-Time system was inserted before or shortly after PCI. The CGM readings were not made available to the treating physician and the patient. If patients had glucose levels above 15 mmol/l during 3 consecutive routine glucose measurements, standard practice at our institution indicated that therapy should be started. To minimize bias, responsibility for the initiation or adjustment of insulin remained with the treating physician or consulting internal medicine physician. All patients were instructed not to consume snacks in between the regular meals provided by the hospital.

In both groups the CGM was calibrated according to manufacturers’ instructions using venous blood samples every 6 hours. The glucose values for calibration were determined using the Accu-Check Inform® (Roche Diagnostics, Basel Switzerland). In the SAP group, additional calibrations were performed if there was a false alarm (Appendix I). Routine venous blood samples for glucose determination were taken before PCI and at 24 and 48 hours after admission. Blood was collected in heparine gel tubes and centrifuged for 10 min at 1600 x g and 18° C for immediate glucose determination.

Outcome measures and statistical analyses
The main outcome measure was the proportion of time spent hyperglycaemia (>=7.8 mmol/l) as measured by continuous subcutaneous glucose monitor (CGM) during 48 hours. Also we calculated the proportion of time spent in hypoglycaemia
(<=3.9 mmol/l), spent within the initial alarm target range (4.7-6.1 mmol/l) and the Area Under the Curve (AUC) for hypo- and hyperglycaemia.

Differences in plasma glucose values during admittance were assessed. Furthermore we calculated CGM accuracy with the mean absolute difference (MAD). The standardised venous recalibration samples taken every 6 hours were compared with the last sensor value before recalibration (MAD = |CGM value - blood glucose| / blood glucose). Thus, we did not use the additional calibration values performed in the SAP group in case of a false alarm. Finally, the number of alarms to which the nursing staff had to respond in the SAP group was assessed as well as the number of hypoglycaemic episodes (plasma glucose <=3.9 mmol/l) that were followed by oral or intravenous glucose administration.

A formal power analysis was not possible, because this is the first study applying SAP in the CCU. Therefore, we aimed to include 20 patients to be randomised in a 1:1 ratio. Results were presented as mean ± SD or median with IQR were appropriate. For the between group differences from the sensor derived endpoints, we used the Mann-Whitney-U test or the student T test. The between group difference for the plasma glucose values were tested using an ANOVA model for repeated measurements. All analyses were performed in SPSS 16.0 (SPSS Inc., Chicago, IL, USA).

RESULTS

After screening 45 patients we randomised 20 patients to either 48 hours of SAP therapy or standard care. In both the SAP group and Control group one patient dropped-out because of transferral to another hospital. In the Control group, one patient withdrew informed consent. Thus 9 and 8 patients were eligible for analyses in the SAP- and Control group, respectively. All patients resumed eating regular meals after admission. The baseline characteristics are provided in Table 1. The median amount of IV insulin given as a bolus before PCI in the SAP group was 3.6 IU (IQR 3.3-4.8). Hereafter, 102.9 IU (IQR 67.6 to 147.3) were given subcutaneously with the insulin pump, of which 82% (IQR 69-92) was basal insulin. In the Control group no insulin therapy was initiated by the treating physician. The median treatment time the SAP group was 47.0 hours (IQR 46.2 to 48.0) and in the Control group 44.6 (IQR 22.0 to 48.6), p=0.67. Figure 2 shows the median glucose values for both groups as measured every 5 minutes by the CGM system (2 hours after initiation).
Sensor augmented pump therapy to treat hyperglycaemia at the CCU

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<th>Control group (n=8)</th>
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<td>HbA1c (median, IQR)</td>
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Table 1: Cohort characteristics, SAP=Sensor Augmented Pump, MI= Myocardial Infarction, CAD= Coronary Artery Disease, LAD= Left Anterior Descending, RCA= Right Coronary Artery, LCX= Left Circumflex

![Figure 2: median sensor glucose values every 5 minutes after start measurements sensor for both groups. SAP= Sensor Augmented Pump](image-url)
The percentage of time spent in hyperglycaemia during the 48 hours after PCI was significantly smaller in the SAP group: 14.6% (IQR 10.5 to 18.5) vs. 36.3% (IQR 26.0 to 80.4), \( p<0.01 \). The proportion of time spent in hypoglycaemia was significantly greater in the SAP group (8.9%, IQR 8.3 to 12.5) as compared to the Control group (0%, IQR 0 to 1.5), \( p<0.001 \) and the percentage of time spent in the initial alarm target range of 4.7 to 6.1 mmol/l was 32.7% (IQR 28.4 to 36.0) in the SAP group and 2.2% (IQR 0.2 to 27.7) in the control group, \( p=0.036 \). The AUC for hyperglycaemia was significantly smaller in the SAP group (0.1 mmol/l/min, IQR 0.0 to 0.1) as compared to the Control group (0.2 mmol/l/min, IQR 0.1 to 0.4), \( p=0.015 \). When comparing the AUC for hypoglycaemia this was 0.02 mmol/l/min (IQR 0 to 0.02) in the SAP group and 0 mmol/l/min (IQR 0 to 0) in the Control group, \( p<0.01 \).

The median plasma glucose in the SAP group decreased from 10.3 mmol/l (IQR 9.0 to 13.1) pre-PCI to 4.8 mmol/l (IQR 4.0 to 7.4) after 24 hours and 4.6 mmol/l (IQR 4.2 to 7.1) after 48 hours (Figure 3). In the Control group, the median glucose pre-PCI was 9.1 mmol/l (IQR 8.6 to 11.4), which decreased to 7.7 mmol/l (IQR 6.3 to 10.5) after 24 hours and 6.9 mmol/l (IQR 6.1 to 11.5) after 48 hours. The plasma glucose in the SAP group decreased significantly more as compared to the Control group, \( p=0.025 \).
In total we measured 7620 valid sensor values during the study. In 6% of the monitoring time the sensor did not generate a signal. On four occasions a sensor had to be replaced because of sensor failure. The mean number of calibrations per 24 hours was 9 (±4) in the SAP group and 4 (±1) in the Control group and the median number of paired regular calibration values (every 6 hours) per patient was 5 (IQR 4-6.5). The accuracy of the CGM based on the regular calibration values did not differ significantly between both groups with an MAD of 21.6% (±9.6) in the SAP group and 18.5% (±8.8) in the control group (p=0.50).

In the SAP group, the nursing staff responded 11 times (±6) per 24 hours to an alarm, with an equal distribution between the hypo- and hyperglycaemic alarms. In the majority of the cases, the patient needed to indicate that the alarm was going off because the acoustic signal was too weak to be heard by the nurse on the coronary care unit. The basal rate was adjusted 9 times (±5, mean ± SD) per 24 hours. The BolusWizard® advice was followed 75% of the time. In 25% of the time the advised amount of insulin was lowered by the study staff. In the SAP group, hypoglycaemia (plasma glucose <=3.9 mmol/l) followed by glucose administration occurred 11 times in 6 patients. Of these, 3 patients had known diabetes. All events were without clinical sequelae and occurred at least 23 hours after admission with a median temporary distribution of 31.4 hours (IQR 26.7-36.6) after admission. In the Control group, no hypoglycaemia was observed. No other device related adverse events occurred.

DISCUSSION

In this randomised controlled trial we showed that sensor augmented insulin pump therapy in patients with STEMI and admission hyperglycaemia lowered the proportion of time spent in hyperglycaemia. This was accompanied by a significant increase in the percentage of time in normoglycaemia, but also an increase in hypoglycaemia and workload.

The (CREATE)-ECLA, Pol-GIK and GIK trials all aimed to deliver high concentrations of insulin in glucose-insulin-potassium solution to patients with AMI, without lowering the mean glucose levels.19-21 All of these trials yielded negative results. In patients with diabetes mellitus, the first DIGAMI trial successfully lowered the glucose during admittance and thereafter, thereby improving survival.6 Targeting the mean glucose in the CCU seems more important than the administration of insulin, as also indicated by Kosiborod and colleagues.9 In contrast with the DIGAMI 2 and HI-5 trial, we were able to lower median
glucose values during CCU admittance after STEMI. The reduction of the proportion of time spent in hyperglycaemia that we found was also shown in the trials investigating SAP therapy in diabetes mellitus type 1 patients. An increase in hypoglycaemia is not a consistent finding in these trials; however they all concern intensively insulin treated type 1 patients, with hypoglycaemia occurring in both arms of the studies. In our study, only the SAP group received strict glucose control with ensuing hypoglycaemia.

The use of a continuous glucose sensor in a CCU setting was investigated before in an exploratory study by Rowen and colleagues. They concluded that the use of CGM was helpful to the nursing personnel, without an increase in workload. This is in contrast with our findings, as most of the personnel indicated that the workload substantially increased due to SAP treatment. Besides paying attention to CGM alarms and checking the plasma glucose, the nursing staff had to follow the treatment algorithm and perform calibrations at set times. The number of alarms to which the nursing staff had to respond was experienced as high (11 times per 24 hours). To decrease the workload, we changed the alarm thresholds for the hyperglycaemic alarm during the trial. One important explanation for the false positive or negative alarms is the inaccuracy of the interstitial glucose measurements as compared to the plasma glucose. In our trial we found the MAD to be 18.5 to 21.5%. It should be noted that we used venous plasma samples to determine the glucose calibration values, whereas the usual outpatient practice is to calibrate against capillary blood. However, our results are in line with previous studies investigating the CGM in the ICU. The somewhat higher calibration rate in the SAP group did not lead to a different accuracy of CGM measurements in both groups, which may be due to the fact that sensor accuracy is more influenced by the timing rather than the frequency of the calibration. We only calibrated the sensor when glucose values were stable and the patient was not eating.

On many occasions, the patient had to alert the nurse that an alarm was signalling. It is therefore likely that not all alarms were addressed immediately and this could have contributed to the hypoglycaemia developed in 6 patients. The observation that the acoustic signal of the SAP is not loud enough in the hospital setting has also been made by Logtenberg et al. We have however used a device designed for treatment in the outpatient setting and necessary adjustments for the in-hospital setting were to be expected.

Due to logistic reasons we were not always able to complete the 48 hours of treatment time. Figure 3 clearly shows that the median sensor value lines meet before completion of the preset 48 hours of intervention. Although this is a
limitation of the trial, plasma glucose in SAP was lower as compared to the Control group up to 48 hours.

Because this was a pilot trial, it was limited by its relative small sample size. Therefore, despite appropriate randomisation procedures, the percentage of patients with diabetes mellitus was almost twice as high in the SAP group (44%) as compared to the Control group (25%), which was also reflected in a higher admission glucose and HbA1c in the SAP group. However, despite this baseline difference putting the SAP group at the disadvantage, glucose in the SAP group was significantly lower as compared to the Control group in the first 48 hours. Notably, there was also a spontaneous glucose decrease in the Control group from baseline to 48 hours.

This is the first randomised controlled pilot trial showing that in hyperglycaemic STEMI patients, SAP clearly significantly reduces the duration of hyperglycaemia as well as plasma glucose levels, when compared with hyperglycaemic control patients. This is however accompanied by a small but significant increase of hypoglycaemia and considerable workload for the nursing staff. Accuracy and alarm functions need improvement in this setting. Although a promising tool for in-hospital hyperglycaemia therapy SAP needs improvement, especially with regard to sensor accuracy and the alarm function of the device, before continuing to large scale randomised controlled trials.

ACKNOWLEDGEMENTS

We thank Medtronic International Trading Sàrl for providing the sensors for this investigation free of charge.
REFERENCES


Sensor augmented pump therapy to treat hyperglycaemia at the CCU


Check the plasma blood glucose

1. Snooze the alarm
2. Use the plasma glucose value to adjust the basal insulin rate
3. Calibrate the device*

* Only perform calibrations when the patient is not eating and when the sensor indicates stable glucose values.

Alarm

BG = blood glucose

BG < 4.7
BG 4.7 - 6.1
BG > 6.1

APPENDIX 1 - Insulin algorithm (Chapter 9)
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<td>0.4</td>
<td>0.5</td>
<td>0.6</td>
<td>0.7</td>
<td>0.8</td>
<td>0.9</td>
<td>1.0</td>
</tr>
<tr>
<td>&lt; 3.3</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
<td>0.0</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Glucose range (mmol/L)</th>
<th>Advice</th>
<th>Specific</th>
<th>General</th>
</tr>
</thead>
<tbody>
<tr>
<td>16.1 - &gt; 25</td>
<td>Check ketones at glucose &gt; 16.7 mmol/L</td>
<td>If glycaemic range has been lowered: remain in same column</td>
<td></td>
</tr>
<tr>
<td>6.2 – 16.0</td>
<td>-</td>
<td>-</td>
<td>If glycaemic range unaltered: move 1 column to the right</td>
</tr>
<tr>
<td>4.7 – 6.1</td>
<td>-</td>
<td>-</td>
<td>If glycaemia remains within this zone: stay in same column</td>
</tr>
<tr>
<td>&lt; 3.3 – 4.6</td>
<td>-</td>
<td>-</td>
<td>If glycaemia &lt; 4.7 mmol/L: move 1 column to the left</td>
</tr>
<tr>
<td>Consult doctor if E/u =&gt; 24.0</td>
<td>-</td>
<td>-</td>
<td></td>
</tr>
</tbody>
</table>

Glucosaemia (mmol/l) | Glucose 30% | Action |
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>3.3 - 3.8</td>
<td>20 ml</td>
<td>o Move 1 column to the left</td>
</tr>
<tr>
<td>2.8 - 3.3</td>
<td>30 ml</td>
<td>o Re-check BG after 15 min</td>
</tr>
<tr>
<td>&lt; 2.8</td>
<td>40 ml</td>
<td>o BG 2x &lt; 3.3 mmol/L: consult doctor</td>
</tr>
</tbody>
</table>

Intravenous starting insulin bolus pre-PCI:

- Only for patients randomised to the sensor augmented pump group
- Determine the starting rate in K2, - Multiply by 1.5, - Give I.V.
No apparent local effect of insulin on microdialysis continuous glucose monitoring measurements

J Hermanides, IME Wenthold, AA Hart, JBL Hoekstra, JH DeVries

Diabetes Care, 2008 Jun;31(6):1120-2
ABSTRACT

**Background** Data investigating the possible disturbing influence of insulin in the vicinity of continuous glucose monitoring (CGM) is lacking. We investigated the hypothesis that high local insulin concentrations would interfere with sensor readings.

**Methods** Two microdialysis sensors were inserted in the periumbilical region of 10 continuous subcutaneous insulin infusion (CSII) treated type 1 diabetes patients. A test sensor was inserted as close as possible to the insulin catheter and compared with a control sensor. Glucose peak and nadir were induced. Horizontal and vertical shifts were assessed using curve fitting and mean absolute difference (MAD) between paired blood and sensor values were calculated.

**Results** Curve fitting showed no significant differences between the two sensors. MAD ± SD was 8.50 ± 3.47% for the test sensor and 9.21 ± 3.17% for the control sensor, \( p=0.72 \).

**Conclusions** Microdialysis CGM can be accurately performed in the proximity of CSII systems.
INTRODUCTION

With ongoing technology development, continuous glucose monitoring (CGM) is expected to work together with continuous subcutaneous insulin infusion systems (CSII), evolving towards closed-loop insulin delivery. According to manufacturers’ instructions, the distance between the insertion points of the pump catheter and the CGM catheter should be more than 2-3 inches. However, no clear evidence supports this. We therefore investigated the hypothesis that high local insulin concentrations would interfere with sensor readings.

RESEARCH AND DESIGN METHODS

Patients with at least 6 months of CSII experience were included. Exclusion criteria were BMI >30 kg/m²; heparin, oral anticoagulant, or corticosteroid use; pregnancy or breastfeeding; and skin problems prohibiting needle insertion. After local ethics committee approval, participants gave written informed consent. A GlucoDay® S (A. Menarini Diagnostics, Firenze, Italy) microdialysis CGM sensor was inserted in the periumbilical region, and a control sensor was inserted at least 10 cm away from the test sensor. The insulin catheter was inserted parallel and as close as possible to the test sensor. The patient returned after overnight fasting. Blood was sampled in sodium fluoride tubes through an intravenous catheter in the forearm for immediate glucose determination at the laboratory (HK/G-6PD method, Roche/Hitachi). Blood glucose levels were increased by withholding the usual rapid-acting insulin injection, and patients then consumed a standard breakfast, as described previously. Forty minutes after breakfast, an augmented bolus of insulin (mean ± SD 10.7 ± 4.5 IU/kg) was administered. During the whole experiment, basal CSII rates were maintained. Calibration was performed retrospectively, using two venous glucose values from periods with minimal glucose rate of change, before breakfast and at the end of the experiment. Statistical analyses were performed using SPSS version 14.0.0 and package S+ 6.2 was used for curve fitting as previously described. It results in a horizontal and vertical shift for both sensors, indicating sensor delay and drift respectively. For each subject, blood glucose values were paired with concomitant interpolated sensor values from the test and the control sensor. The mean absolute difference (MAD) for each sensor was calculated per subject [sensor value -blood... ]
glucose [blood glucose], averaging the paired data per experiment per sensor. Comparisons of the MADs were made using the Wilcoxon’s signed-rank test.

RESULTS

Out of fifteen performed experiments, five were unsuccessful because of pressure or leakage problems. Results of three female and seven male diabetes type 1 subjects were analysed. Mean age was 50.1 ± 7.9 years (mean ± SD), BMI 24.2 ± 2.6 kg/m², diabetes duration 26.8 ± 9.9 year and HbA₁c 8.4 ± 1.4%. The mean insertion distance between the insulin catheter and the closest insertion point of the microfiber was 0.9 ± 0.2 cm. There was no significant correlation between the insertion distance and the MAD of the test sensor (r =-0.12). The curves from the ten successful experiments are shown in Figure 1. Bland-Altman plots are provided in Figure 2.

After curve fitting, there is evidence that the test sensor values trail those of the blood glucose by an average -10.8 ± 4.0 min (range of –18.2 to -6.0 min, one-sample t test: p<0.001). A minus sign indicates a delay with respect to the blood glucose curve. For the control series, the average delay was: -5.7 ± 8.1 min (–11.8 to 14.8 min, one-sample t test: p=0.053). However, the difference in horizontal shift between both sensors did not reach statistical significance (p=0.13). No significant vertical shifts were detected.
Figure 1: The results of all ten patients are displayed. The continuous line represents the test sensor; the dotted line represents the control sensor and the long dashed line represents the blood glucose values; the time of breakfast is indicated by the arrow.
In total, 374 blood glucose values were paired with the concomitant values from both sensors, with 37 ± 2 paired values per patient. The average MAD calculated from the ten MADs was 9.21 ± 3.17% for the control sensor and 8.50 ± 3.47% for the test sensor (Wilcoxon’s signed-rank test $p=0.72$).

Figure 2- Bland-Altman plots for the control sensor (A) and the test sensor (B). The x-axis represents the average of blood and sensor glucose measurements, and the y-axis represents the difference between sensor and paired blood glucose (BG) measurements as proportion of the average BG measurement. The difference between BG and sensor readings is 0 at the horizontal solid line. The long dashed line represents the mean difference (−0.0014 for the control and −0.024 for the test sensor); dotted lines are drawn at the mean difference ± 1.96 times the SD of the differences.
CONCLUSIONS

We investigated the hypothesis that high local insulin concentrations would interfere with sensor readings by infusion of insulin in the proximity of a microdialysis type glucose sensor. No difference in MAD was detected when comparing the test and control sensors. When applying curve fitting, there was a significant delay (mean ± SD 10.8 ± 4.0 min) of the test sensor compared to the blood glucose values. A non-significant delay was found for the control sensor (5.7 ± 8.1 min). This cannot be fully explained by instrumental delay.4,5 One could hypothesise that insulin induced saturation of the low number of GLUT4s present at the adipocyte cell surface could explain how glucose can reliably be measured in the vicinity of relatively high insulin concentrations and possibly delay glucose-transporting capacity.6 This speculation merits further investigation. However, to minimize variation, we have used the same devices for the test and control sensors and bias created due to constant intersensor variability can therefore not be excluded.7 A preliminary human pilot study also suggested no local influence of insulin on sensor readings in humans.8 Furthermore, the relatively low number of 23 hypoglycaemic paired readings is a limitation of this study and the efficacy of the test sensor in the hypoglycaemic range needs further investigation.

We aimed to position the tip of the injection catheter as close to the microdialysis catheter as possible. Using ultrasound, we were not able to visualize the microfiber subcutaneously. Therefore we can not tell the exact distance between the injection and microdialysis sites, but is seems likely that the actual distance was smaller than the surface distance of the two insertions.

We conclude that microdialysis CGM can be accurately performed at a mean distance of 0.9 cm from a CSII system in the normo- and hyperglycaemic ranges and probably the hypoglycaemic range during rapid rise and fall of blood glucose. This has important consequences for the use of CGM in type 1 diabetes and the development of a closed-loop system. Further studies should focus on a possible additional sensor delay caused by insulin and evaluate sensor accuracy in the proximity of insulin during hypoglycaemia.

ACKNOWLEDGEMENTS

We acknowledge Nico J. Smits for his expert ultrasound help.
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Postprandial glycaemic excursions with the use of a closed-loop platform in diabetes type 1, a pilot study

AC van Bon, J Hermanides, R Koops, JBL Hoekstra, JH DeVries

Submitted for publication
ABSTRACT

**Background** To evaluate the efficacy of a proportional derivative algorithm closed-loop system to control postprandial glucose concentrations in diabetes type 1.

**Methods** Six patients treated with CSII received a standardised meal on three days. The first day served as control, the second day as learning experiment for the algorithm and the third day to compare the closed-loop to the control day. Venous glucose was measured as reference until 300 minutes postprandially. The artificial pancreas platform consisted of a subcutaneous continuous glucose monitor (CGM), the GlucoDay® S (Menarini Diagnostics), two D-Tron+ pumps (Disetronic Medical Systems) for subcutaneous insulin and glucagon administration connected to a personal computer.

**Results** One patient was excluded due to technical failure of the CGM. Two of five patients were male; mean age was 50.8 years (range 38 to 60) and mean HbA1c 8.7% (range 7.0 to 12.2). The median postprandial venous glucose concentration of day 1 was 11.4 mmol/l (range 5.2 to 14.7 mmol/l) compared to 8.7 mmol/l (7.1 to 8.8 mmol/l) on day 3 ($p=0.14$). Percentage of time spent in postprandial euglycaemia on day 1 was 31% versus 60% on day 3 ($p=0.08$). Time spent below 3.9 mmol/l was 19% on day 1 compared to 11% on day 3 ($p=1.0$). Time above 10 mmol/l on day 1 was 60% versus 29% on day 3 ($p=0.22$).

**Conclusion** The artificial pancreas provided comparable postprandial glycaemic control as usual care.
INTRODUCTION

Continuous subcutaneous insulin infusion (CSII) combined with continuous glucose monitoring (CGM) and a glucose control algorithm would result in an artificial pancreas. Artificial pancreas or closed-loop systems are capable to achieve automated glucose control in ICU or CCU settings. Steil and Weinzimer tested a subcutaneous artificial pancreas based on a proportional integrated derivative (PID) model in a clinical research unit. Mean glucose concentrations were not different from usual care; however postprandial glucose excursions were higher than with usual care. A manually administered premeal priming bolus could partially overcome this problem. Schaller et al. evaluated an algorithm based on model predictive control (MPC) in six patients with diabetes type 1 during eight hours in the fasting condition. The model normalised glucose concentrations if the glucose level was above 6 mmol/l and then maintained normoglycaemia. Hovorka et al. evaluated glucose control with an algorithm based on a MPC model in patients with diabetes type 1 compared to usual care with an insulin pump in three different settings: overnight glucose control starting two hours after dinner following a pre-meal with self-determined manual insulin bolus until the next morning, postprandial glucose control 30 minutes after dinner comparing rapidly absorbed carbohydrates to slowly absorbed carbohydrates until the next morning and glucose control starting two hours after 45 minutes of exercise until the next morning. In all these studies closed-loop glucose control resulted in more time in target range as compared to conventional care. Recent data showed similar results for an MPC closed loop artificial pancreas compared to usual care in fourteen patients.

The aim of this study was to test the feasibility of a control algorithm to control postprandial glucose concentrations after a single meal in patients with diabetes type 1.

METHODS

Subjects
Six patients with type 1 diabetes treated with CSII for more than six months, aged 18-70 years were recruited for the study. All patients gave written informed consent. The ethics committee of the Academic Medical Centre at the University of Amsterdam approved the study.
**Study Procedures**

In the afternoon before the study visit, a microdialysis glucose sensor (GlucoDay® S Menarini Diagnostics, Firenze, Italy) was inserted. Patients were admitted to the clinical research unit of the Academic Medical Centre the following morning in fasting condition. An intravenous catheter was inserted into an antecubital vein for blood sampling. During the first test day, the patients administered a self-determined insulin bolus before a standardised meal of 40 gram carbohydrates. During the second and third test day, patients wore two D-Tron+ pumps (Disetronic Medical Systems, St. Paul, MN) for subcutaneous insulin and glucagon administration, respectively. The CGM sensor, insulin pump and the glucagon pump were connected to a personal computer containing the algorithm. The test started after calibration of the CGM. No premeal insulin bolus was administered when the standardised meal was served. The sensor glucose values were read out every ten seconds. Every five minutes an average glucose level was calculated. The second day was a so-called learning day of the algorithm to determine an individual insulin sensitivity factor. This factor was initially calculated on the basis of total daily insulin need and adjusted as needed during the day 2 experiment. During all three test days, venous glucose was measured at baseline and every 30 minutes until five hours postprandially.

**Calibration procedure**

The calibration procedure was performed before starting the artificial pancreas and repeated in case of a difference between sensor glucose and self-monitored glucose level above 1.5 mmol/l. The calibration procedure consisted of three measurements of the sensor glucose and the corresponding concomitant self-monitored glucose values with an interval of ten minutes. The average difference of the three measurements between the sensor glucose level and the self-monitored glucose was calculated. This average was the correction factor for the sensor glucose.

**Algorithm**

The control algorithm, employed in this study was designed by Inreda BV (Goor, the Netherlands) and is patented (NL C 1032756; WO 2007/049961 A3). The algorithm can be characterised as a self learning individualised proportional derivative controller. Insulin delivery is determined by the difference between current and target glucose and the rate of change of glucose levels. Furthermore, insulin delivery is adjusted for individual insulin sensitivity. Target blood glucose values can be programmed for a lower and an upper limit. The upper limit was set...
Algorithm to treat postprandial glycaemic excursions in a closed-loop format

at 7 mmol/l and the lower limit at 5 mmol/l. Every five minutes, the glucose levels are compared to the target range. There are three operating ranges. First, if glucose values are below the lower limit, a sound signal is generated. The patient can correct the low glucose value by eating. In case of a glucose fall below a next limit, glucagon is injected according to a formula taking into account the rate of glucose fall. During the experiment, this was set at 3.2 mmol/l. If glucose levels are between the lower and upper limit, no insulin is administered by the algorithm. If glucose levels are above the upper limit, insulin is injected according to a formula taking into account the rate of glucose rise. Every seven minutes, insulin is administered if the glucose levels are above the limit and not falling. If glucose concentration is above 20 mmol/l, the maximum insulin administration rate is reached i.e. 10 units per seven minutes.

Statistics
All postprandial venous glucose concentrations on the first day and on the third day were averaged per patient and were compared as paired measurements with the Wilcoxon Signed Ranks test. Median venous glucose concentrations are given with minimum and maximum value. Sensor glucose concentrations were calculated every three minutes. The median sensor glucose concentration is expressed as area under the curve (AUC). Demographic features are given as mean with range of minimum and maximum. Time spent in euglycaemia was defined as the percentage of time the glucose concentrations were between 3.9 mmol/l and 10.0 mmol/l.

RESULTS
Due to failure of the microdialysis filament on day 3, one male patient was excluded. Two of five patients were male; mean age was 50.8 years (range 38 to 60) and mean HbA1c 8.7% (range 7.0 to 12.2). The mean diabetes duration was 30.3 years (range 14 to 45) and the mean CSII duration was 6.7 years (range 2 to 14, Table 1).

<table>
<thead>
<tr>
<th>Table 1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline characteristics (n=5)</td>
</tr>
<tr>
<td>Male / Female</td>
</tr>
<tr>
<td>Age, years (mean, range)</td>
</tr>
<tr>
<td>HbA1c, % (mean, range)</td>
</tr>
<tr>
<td>Diabetes duration, years (mean, range)</td>
</tr>
<tr>
<td>CSII duration, years (mean, range)</td>
</tr>
</tbody>
</table>
The median venous glucose concentration on day 1 was 11.4 mmol/l (range 5.2 to 14.7 mmol/l) compared to a median venous glucose concentration in day 3 of 8.7 mmol/l (range 7.1 to 8.8 mmol/l), \( p=0.14 \) (see Figure 1 and Table 2). For those with HbA1c >7%, \( n=4 \), the median glucose concentration on day 1 was 12.6 mmol/l (range 9.2 to 14.7 mmol/l) compared to 8.7 mmol/l (range 8.5 to 8.8 mmol/l) on day 3, \( p=0.07 \). The AUC of the sensor glucose concentration of day 1 (2993 mmol/l x minutes, range 1900 to 4581) did not differ from day 3 (2746 mmol/l x minutes range 2426 to 3330), \( p=0.5 \). The venous peak and nadir glucose concentration on day 1 and day 3 were not different (Table 2).

**Figure 1** - median venous glucose concentrations day 1 compared to day 3

![Figure 1](image)

**Table 2** - postprandial glucose values day 1 compared to day 3, \( n=5 \)

<table>
<thead>
<tr>
<th>Plasma glucose, mmol/l (median, range)</th>
<th>Day 1</th>
<th>Day 3</th>
<th>( p )-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>11.4 (5.2 to 14.7)</td>
<td>8.7 (7.1 to 8.8)</td>
<td>0.14</td>
</tr>
<tr>
<td>t=120 min</td>
<td>12.3 (4.2 to 17.4)</td>
<td>8.1 (6.8 to 9.6)</td>
<td>0.23</td>
</tr>
<tr>
<td>t=180 min</td>
<td>13.4 (3.3 to 15.6)</td>
<td>4.5 (3.3 to 9.0)</td>
<td>0.08</td>
</tr>
<tr>
<td>Peak</td>
<td>14.1 (7.9 to 17.7)</td>
<td>14.5 (10.8 to 17.7)</td>
<td>0.5</td>
</tr>
<tr>
<td>Nadir</td>
<td>10.4 (3.0 to 10.1)</td>
<td>3.8 (3.2 to 4.4)</td>
<td>0.08</td>
</tr>
</tbody>
</table>
On day three, the patients tended to have a higher percentage of time spent in euglycaemia measured by venous glucose measurements compared to day 1 (31% vs 60%, \( p=0.08 \)). No significant differences were seen in time spent in hypoglycaemia or hyperglycaemia between day 1 and day 3.

On day 3, three hypoglycaemic episodes occurred in two patients lasting 6, 9 and 30 minutes. During the period of 30 minutes, the corresponding venous blood glucose level was 3.2 mmol/l. No venous measurements were taken during the other two periods. In addition, venous glucose measurements detected five other episodes of glucose levels below 3.9 mmol/l, in three patients, with values of 3.2, 3.6 (twice) and 3.8 mmol/l (twice). All hypoglycaemic periods occurred late postprandially, after 150 minutes or more.

On day 3, the algorithm was enabled to give alarms. The number of sound alarms and number of the glucagon responses are shown in table 3. In total the sound alarm went off 14 times, range 1-4 per patient. Glucagon boluses were given in two patients. No nausea was noted.

The cumulative mealtime related insulin requirements on day 1 and day 3 are shown in table 3. No significant differences were seen, \( p=0.14 \).

**Table 3a**- insulin need during the study, given as international units

<table>
<thead>
<tr>
<th>Patient</th>
<th>Day 1</th>
<th>Day 3</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Bolus</td>
<td>Basal</td>
</tr>
<tr>
<td>1</td>
<td>14</td>
<td>6.1</td>
</tr>
<tr>
<td>2</td>
<td>4</td>
<td>3</td>
</tr>
<tr>
<td>3</td>
<td>4</td>
<td>5</td>
</tr>
<tr>
<td>4</td>
<td>4.5</td>
<td>5.8</td>
</tr>
<tr>
<td>6</td>
<td>5</td>
<td>6.1</td>
</tr>
</tbody>
</table>

**Table 3b**- number of sound alarms (glucose<5 mmol/l) and the number of glucagon responses (glucose<3.2 mmol/l)

<table>
<thead>
<tr>
<th>Day 3</th>
<th>Hypoglycaemic alarm</th>
<th>Glucagon need (IU)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Patient 1</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Patient 2</td>
<td>4</td>
<td>10</td>
</tr>
<tr>
<td>Patient 3</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Patient 4</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>Patient 6</td>
<td>2</td>
<td>1</td>
</tr>
</tbody>
</table>
DISCUSSION

In this small pilot study, the feasibility of a closed-loop artificial pancreas based on a PID algorithm was tested. Postprandial venous glucose control was comparable to usual care, with a tendency to a higher percentage of time spent in euglycaemia. We don’t want to overemphasise this, as in some of our patients with relatively high HbA1c’s control could have been optimised using conventional methods, but for a first pilot trial we chose to take these real-life patients as a starting point.

Preliminary results of closed-loop artificial pancreas experiments based on Model Predictive Control (MPC) also showed comparable control during 22 hours closed-loop versus usual care. Postprandial hyperglycaemia did not significantly differ between closed-loop and usual care, but the maximum glucose levels were above the postprandial targets advised by the American Diabetes Association (ADA). Weinzimer et al. also reported high postprandial levels that could partially overcome by a manual premeal insulin bolus. In our pilot study the postprandial glucose values achieved by the AP were almost within the postprandial range of the ADA (<10 mmol/l). The median venous glucose on day 1 time point 120 minutes postprandial was 12.3 mmol/l (range 4.2 to 17.4 mmol/l) versus median glucose 8.1 mmol/l on day 3 (range 6.8 to 9.6 mmol/l), \( p=0.23 \). At time point 180 minutes postprandial, the median venous glucose concentrations was 13.4 mmol/l on day 1 (range 3.3 to 15.6 mmol/l) and 4.5 mmol/l on day 3 (range 3.3 to 9 mmol/l), \( p=0.08 \) (Table 2).

After the learning day, the individual sensitivity was adjusted for the following test day. Probably, the individually adjusted insulin sensitivity factor is an explanation for the tendency towards lower glucoses on day three compared to day one. The research groups of Padova, Montpellier and Virginia also used an individual factor. This factor named ‘aggressiveness’ or ‘q’ was dependent of clinical parameters of the patient. The research groups did not have a learning day, so q was not adjusted during the experiment.

To prevent hypoglycaemias, the hypoglycaemic alarm was set at 5 mmol/l. If the glucose level was below 5 mmol/l a hypoglycaemic alarm went off and patients had to eat 25 gram carbohydrates. All patients had to eat carbohydrates, but the alarm was not followed by oral carbohydrates if the alarm went off within 5 until 10 minutes after eating.

A hypoglycaemia was defined as a glucose concentration below 3.9 mmol/l. On day 3, five episodes of hypoglycaemia were measured by venous glucose concentrations
in three patients, one patient encountering a single value of 3.8 mmol/l only, of arguable significance. All events occurred late postprandial, between 150 and 300 minutes. The lowest measured venous blood glucose concentration was 3.2 mmol/l. This occurred in two patients and glucagon injections were administered. In one of these two patients the amount of insulin administered on day 3 was substantially larger than on day 1. So, in these two patients the individual sensitivity factor was set too aggressive. One other patient received four times more insulin than usual. Taking her HbA1c of 10% into account, her daily insulin doses was probably too low.

Glucagon boluses were given in two patients in order to prevent severe hypoglycaemia. The efficacy of low dose glucagon as a rescue to prevent severe hypoglycaemia remains to be shown in subsequent experiments. Damiano et al 10 also used subcutaneous glucagon injections in their closed-loop glucose control, but glucagon was used to control the glucose concentration within the normal range with frequent injection of small doses, while it was used as rescue compound in our system.

In the near future, the algorithm will undergo revisions, mainly at the glucose level of the sound alarm. The slope of the glucose drop has to be taken in account if the carbohydrate alarm will go off, and the level will be set lower, probably at 4 or 4.5 mmol/l. Also a needle type sensor will replace the microdialysis sensor because of the technical problem of the microdialysis filament. Furthermore, the examination time and number of patients will be extended. Hereafter, a wireless connection between the components would enable outpatient testing.

In conclusion, postprandial glucose control by this algorithm was feasible, and comparable to non-optimised usual care.
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(10) Model predictive closed loop control with insulin and glucagon. EASD / JDRF symposium EASD 2009 S13; 2009.
Glucose variability is associated with ICU mortality

J Hermanides, TM Vriesendorp, RJ Bosman, DF Zandstra, JBL Hoekstra, JH DeVries

Critical Care Medicine, 2010 Mar;38(3):838-42
ABSTRACT

Objective Mounting evidence suggests a role for glucose variability in predicting intensive care unit (ICU) mortality. We investigated the association between glucose variability and intensive care unit and in-hospital deaths across several ranges of mean glucose.

Design Retrospective cohort study.

Setting An 18-bed medical/surgical ICU in a teaching hospital.

Patients All patients admitted to the ICU from January 2004 through December 2007.

Measurements and Main Results Two measures of variability, mean absolute glucose change per hour and SD, were calculated as measures of glucose variability from 5728 patients and were related to ICU and in-hospital death using logistic regression analysis. Mortality rates and adjusted odds ratios for ICU death per mean absolute glucose change per hour quartile across quartiles of mean glucose were calculated. Patients were treated with a computerized insulin algorithm (target glucose 4.0 to 7.0 mmol/l). Mean age was 65 ± 13 years, 34% were female, and 6.3% of patients died in the ICU. The odds ratios for ICU death were higher for quartiles of mean absolute glucose change per hour compared with quartiles of mean glucose or SD. The highest odds ratio for ICU death was found in patients with the highest mean absolute glucose change per hour in the upper glucose quartile: odds ratio 12.4 (95% confidence interval, 3.2 to 47.9; p<0.001). Mortality rates were lowest in the lowest mean absolute glucose change per hour quartiles.

Conclusions High glucose variability is firmly associated with ICU and in-hospital death. High glucose variability combined with high mean glucose values is associated with highest ICU mortality. In patients treated with strict glycaemic control, low glucose variability seemed protective, even when mean glucose levels remained elevated.
INTRODUCTION

The results of the Leuven studies have led to a worldwide increase in the implementation of strict glycaemic control in the intensive care unit (ICU). The mortality reduction in these landmark trials was attributed to the strict lowering of mean glucose (target 4.4-6.1 mmol/l) during admission in the intervention group. Interestingly, the positive results of the Leuven studies have not been reproduced in later studies. It is therefore of importance to examine whether factors other than mean glucose are of influence. As mean glucose is lowered and glycaemic excursions are targeted, glucose variability (GV) is likely to be reduced as well. Several studies have shown that GV is strongly associated with short-term ICU mortality. This can be understood from a pathophysiological viewpoint, because hyperglycaemia, as well as GV, can contribute to ICU mortality by increasing oxidative stress, neuronal damage, mitochondrial damage and coagulation activation. In a study by Krinsley in an ICU population, the SD as marker of GV was a predictor of mortality within different ranges of mean glucose and a stronger predictor than mean glucose itself. However, the SD is not the most appropriate method for defining GV of repeated glucose measurements. Two patients with the same mean glucose and SD can express completely different patterns of variability (Figure 1). Furthermore, the majority of the results gathered so far on the predictive value of GV come from populations that are not treated or are partly treated with strict glycaemic control.

The aims of this study were to measure GV over time in a large strict glucose control-treated ICU population across several ranges of mean glucose, and to investigate the association of GV and mean glucose values with ICU- and in-hospital mortality.

Figure 1 - two fictive patients with identical mean glucose and SD, but different patterns of variability, expressed by the mean absolute glucose change (MAG)
MATERIALS AND METHODS

Setting
We performed a retrospective cohort study in an 18-bed medical/surgical ICU in a teaching hospital (Onze Lieve Vrouwe Gasthuis Hospital, Amsterdam, The Netherlands). On average, a nurse takes care of two patients, depending on the severity of disease. All beds were equipped with a clinical information system (iMD-Soft; MetaVision, Tel Aviv, Israel) and all clinical and laboratory data was stored here. The glucose regulation protocol was implemented in April 2001 and set at a target glucose range of 4.0 to 7.0 mmol/l. Using a sliding scale computerised algorithm, the nursing staff was instructed to adjust the insulin infusion rate depending on the current glucose value and the rate of glucose change (based on the previous five measurements). The software also provided the time the next glucose measurement was due, which could vary from 15 minutes up to 4 hours. Routinely, enteral feeding was started within 24 hours after admission, aiming at 2000 ml within 48 hour or 1500 ml within 24 hours. A duodenal feeding tube was inserted in case of persistent gastric retention. When patients resumed normal eating, the tight glucose algorithm was deactivated. The successful implementation of the algorithm has been reported previously. An integrated decision support module controlled the algorithm and was connected to the clinical information system. Because a retrospective analysis of anonymised data was performed, informed consent was not required according to Dutch Ethical Review Board regulations.

Cohort and Data collection
We extracted data from the clinical information system concerning patients admitted between January 2004 and December 2007. Readmissions, patients with a withholding care policy and patients with <3 glucose values measured during admission were excluded. We assessed demographic variables, medical history and mortality in the ICU and in-hospital mortality. Furthermore we collected information on severity of disease, the occurrence of severe hypoglycaemia (glucose <= 2.5 mmol/l) and diabetes mellitus, because these variables are associated with GV. As measures for severity of disease we evaluated both the maximal Sequential Organ Failure Assessment (SOFA) score during admission and the Acute Physiology and Chronic Health Evaluation II (APACHE II) score on admission.
Measures of glucose
Glucose was measured from blood samples obtained from an arterial catheter using the Accu-check (Roche/Hitachi®, Basel, Switzerland), a handheld glucose measurement device. Results were automatically stored in the clinical information system. We collected all glucose values measured for every patient and calculated the mean glucose during admission and the SD. To obtain a measure of GV that was less dependent on the mean glucose and took into account all variability over time, we calculated the mean absolute glucose (MAG) change per patient per hour (formula 1). This is done by taking the sum of all absolute glucose changes during admission and dividing this by the total time spent in the ICU in hours.

\[
MAG = \frac{\Delta BG}{\Delta time}
\]

Formula 1: mean Absolute Glucose (MAG) change is the absolute glucose change (\(\Delta BG\)) per hour spent in the ICU (\(\Delta time\))

Statistical analyses
Results are presented as mean ± SD or median with interquartile range (IQR), depending on the distribution of the data. Mean glucose, the glucose SD and MAG change were divided into quartiles. The area under the receiver operating characteristic curve of the MAG change and the SD were calculated and any difference in predictive value was examined using parametrical bootstrapping with 1000 replicates. To select the best measure for disease severity we compared the relations of the APACHE II and maximal SOFA score with ICU mortality in univariate regression analysis. Using multivariate logistic regression, we calculated odds ratios (ORs) for ICU- and in-hospital death for each MAG quartile and corrected for clinical relevant confounders: sex, age, diabetes mellitus, severity of disease, severe hypoglycaemia and mean glucose. In addition, length of stay in the ICU was included as a possible confounder because of its relation to mortality and likely relation to variability, because variability may change over time and the precision of variability assessment depends on the observation time. Also cardiothoracic surgery was included, because mortality in this group is generally lower compared with other surgical patients. Furthermore, several demographic and physiological characteristics of this group differed from the general ICU population, which could be reflected in differences in mean glucose levels and glucose variability.\(^{22}\) Furthermore, we explored differences in predictive value of the MAG in surgical and medical patients, using an interaction term in the multivariate model. Hereafter, we calculated OR's for ICU death and in-hospital death for different ranges of GV, subdivided into quartiles of mean glucose. All
statistical analyses were performed in SPSS 16.0 (SPSS Inc., Chicago, IL) and SAS 9.1 (SAS Institute, Cary, NC).

RESULTS
Between January 2004 and December 2007, there were 6725 ICU admissions. We excluded 656 readmissions, 86 patients with a withholding care policy and 255 patients with <3 glucose value measured during admission, leaving 5728 patients for our analyses. The characteristics of the studied cohort are displayed in Tables 1A and 1B. In total 154189 glucose values were collected, a median of 12 values per patient (IQR 6 to 23) and 11 values per day (IQR 7 to 14).

<table>
<thead>
<tr>
<th></th>
<th>Cardiothoracic surgery (n=3560)</th>
<th>Medical and Other (n=2168)</th>
<th>Total cohort (n=5728)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years (mean ± SD)</td>
<td>67 ± 11</td>
<td>63 ± 17</td>
<td>65 ± 13</td>
</tr>
<tr>
<td>Gender, female n (%)</td>
<td>1106 (31.1%)</td>
<td>865 (39.9%)</td>
<td>1971 (34%)</td>
</tr>
<tr>
<td>APACHE II score on admission (median, IQR)</td>
<td>15 (12 to 17)</td>
<td>20 (15 to 27)</td>
<td>16 (13 to 20)</td>
</tr>
<tr>
<td>Max SOFA score during admission (median, IQR)</td>
<td>5 (4 to 6)</td>
<td>7 (5 to 10)</td>
<td>6 (5 to 7)</td>
</tr>
<tr>
<td>ICU stay, days (median (IQR)</td>
<td>0.9 (0.8 to 1.1)</td>
<td>1.9 (0.8 to 4.4)</td>
<td>1.0 (0.8 to 2.0)</td>
</tr>
<tr>
<td>Diabetes mellitus, n (%)</td>
<td>681 (19.1%)</td>
<td>18 (0.8%)</td>
<td>699 (12.2%)</td>
</tr>
<tr>
<td>Died ICU, n (%)</td>
<td>27 (0.8%)</td>
<td>334 (15.4%)</td>
<td>361 (6.3%)</td>
</tr>
<tr>
<td>Died hospital, n (%)</td>
<td>93 (2.6%)</td>
<td>516 (23.8%)</td>
<td>609 (10.6%)</td>
</tr>
<tr>
<td>Severe hypoglycaemia (≥ 1 event), n (%)</td>
<td>66 (1.9%)</td>
<td>223 (10.3%)</td>
<td>299 (5.2%)</td>
</tr>
</tbody>
</table>

Table 1A- characteristics of the studied cohort; APACHE Acute Physiology and Chronic Health Evaluation, SOFA Sequential Organ Failure Assessment

<table>
<thead>
<tr>
<th></th>
<th>Surgical (n=4409)</th>
<th>Medical (n=1319)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cardiovascular</td>
<td>3895</td>
<td>235</td>
</tr>
<tr>
<td>Sepsis</td>
<td>52</td>
<td>220</td>
</tr>
<tr>
<td>After cardiac arrest</td>
<td>10</td>
<td>287</td>
</tr>
<tr>
<td>Gastrointestinal</td>
<td>235</td>
<td>57</td>
</tr>
<tr>
<td>Haematological</td>
<td>7</td>
<td>7</td>
</tr>
<tr>
<td>Renal</td>
<td>12</td>
<td>26</td>
</tr>
<tr>
<td>Metabolic</td>
<td>7</td>
<td>48</td>
</tr>
<tr>
<td>Neurological</td>
<td>40</td>
<td>150</td>
</tr>
<tr>
<td>Respiratory</td>
<td>151</td>
<td>289</td>
</tr>
</tbody>
</table>

Table 1B- number of patients per APACHE II admission category (surgical/medical)
Measures of glucose and ICU mortality
For the entire cohort, the median glucose SD was 1.8 mmol/l (IQR 1.4 to 2.4 mmol/l) and the median MAG was 0.6 mmol/l/hr (IQR 0.4 to 0.9 mmol/l). The MAG was significantly stronger associated with ICU death compared with the SD in univariate analysis, a difference in area under the receiver operating curve of 5.4% (95% confidence interval [CI], 3.0 to 7.7, \( p<0.001 \)). The ranges of mean glucose quartiles and MAG quartiles with the number of patients per stratum and ICU mortality are shown in Table 2. The highest ICU- and in-hospital mortality was seen in the upper MAG and upper mean glucose quartile with mortality rates of 24.5% and 28.7% respectively (Figure 2). ICU mortality rates in the lowest MAG quartile ranged from 0.7% to 5.2%.

Severity of disease and glucose variability
The OR for death in the highest quartile of the APACHE II score was 33.8 (95% CI 17.9 to 63.8) and 64.8 (95% CI 28.8 to 145.9) for the maximal SOFA score. Thus we corrected for quartiles of maximal SOFA score instead of APACHE II score as a measure of disease severity in our multiple regression model. The median MAG change increased from 0.6 mmol/l/hr (0.3 to 0.9 mmol/l/hr) in the lowest quartiles SOFA quartile to 0.7 mmol/l/hr (IQR 0.4 to 1.0 mmol/l/hr) in the highest SOFA quartile (\( p<0.001 \)). The association of the MAG and ICU mortality did not significantly differ between surgical and medical patients, \( p=0.74 \).
### Table 2

The number of patients per stratum are depicted with the ICU mortality per stratum (n and %). Ranges of quartiles of mean absolute glucose change (MAG) and mean glucose are given.

<table>
<thead>
<tr>
<th>MAG quartiles (mmol/l/hr)</th>
<th>&lt;0.39 (n=1432)</th>
<th>0.39 to 0.60 (n=1432)</th>
<th>0.60 to 0.88 (n=1432)</th>
<th>&gt;0.88 (n=1432)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean glucose quartiles (mmol/l)</td>
<td>&lt;6.92 (n=1432)</td>
<td>6.92 to 7.60 (n=1436)</td>
<td>7.60 to 8.89 (n=1429)</td>
<td>&gt;8.89 (n=1431)</td>
</tr>
<tr>
<td>1st : &lt; 0.39 mmol/l/hr</td>
<td>18/346 (5.2%)</td>
<td>41/485 (8.5%)</td>
<td>41/385 (10.6%)</td>
<td>44/216 (20.4%)</td>
</tr>
<tr>
<td>2nd : 0.39 to 0.60 mmol/l/hr</td>
<td>4/204 (2.0%)</td>
<td>14/402 (3.5%)</td>
<td>24/465 (5.2%)</td>
<td>24/365 (6.6%)</td>
</tr>
<tr>
<td>3rd : 0.60 to 0.88 mmol/l/hr</td>
<td>2/344 (0.6%)</td>
<td>4/236 (1.7%)</td>
<td>13/353 (3.7%)</td>
<td>32/496 (6.5%)</td>
</tr>
<tr>
<td>4th : &gt; 0.88 mmol/l/hr</td>
<td>1/309 (0.3%)</td>
<td>8/229 (3.5%)</td>
<td>87/355 (24.5%)</td>
<td></td>
</tr>
</tbody>
</table>

### Table 3

- Odds ratio (OR) for ICU and in-hospital death per MAG change quartile, adjusted for age, sex, diabetes mellitus, maximal SOFA score, mean glucose, severe hypoglycaemia and cardiothoracic surgery.

<table>
<thead>
<tr>
<th>Quartiles of MAG change</th>
<th>OR ICU death (95% CI)</th>
<th>OR in-hospital death (95 % CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1st : &lt; 0.39 mmol/l/hr</td>
<td>reference</td>
<td>reference</td>
</tr>
<tr>
<td>2nd : 0.39 to 0.60 mmol/l/hr</td>
<td>1.5 (0.9 to 2.5)</td>
<td>1.5 (1.0 to 2.1)</td>
</tr>
<tr>
<td>3rd : 0.60 to 0.88 mmol/l/hr</td>
<td>1.8 (1.1 to 2.9)</td>
<td>1.6 (1.2 to 2.3)</td>
</tr>
<tr>
<td>4th : &gt; 0.88 mmol/l/hr</td>
<td>3.3 (2.1 to 5.4)</td>
<td>2.8 (2.0 to 3.9)</td>
</tr>
</tbody>
</table>

*p for trend <0.001*
Multivariate analyses
The ORs for ICU death and in-hospital death, adjusted for mean glucose and other confounders are displayed in Table 3: in the highest MAG quartile, the OR for ICU death was 3.3 (95% CI 2.1 to 5.4) and for in-hospital death 2.8 (95% CI 2.0 to 3.9). The risk of death increased per MAG quartile (p for trend <0.001). We performed logistic regression, with ICU death as dependent variable and MAG quartiles as the covariate. Per quartile of mean glucose, we calculated ORs for ICU death. We corrected for age, sex, diabetes mellitus, cardiothoracic surgery, severe hypoglycaemia, length of ICU stay and maximal SOFA score during admission. The highest OR for ICU death was found in patients with the highest MAG in the upper glucose quartile: OR 12.4 (95% CI 3.2 to 47.9, p<0.001). Also in the first quartile of mean glucose, high MAG change in the fourth quartile was associated with ICU death, with an OR of 4.1 (95% CI 1.9 to 9.1, p<0.001). Finally, we performed analyses for in-hospital death. In each quartile of mean glucose, the upper MAG quartile seemed predictive of in-hospital death compared to the first quartile, with ORs for in-hospital death of 2.7 (95% CI 1.6 to 5.2), 1.9 (95% CI 0.9 to 4.2), 2.5 (95% CI 0.9 to 6.8) and 6.4 (95% CI 2.7 to 15.0) across the first, to the fourth mean glucose quartile, respectively.

DISCUSSION

In this retrospective cohort study we have shown that GV, expressed as MAG, is highly associated with ICU death in both high and low ranges of mean glucose. In combination with a high mean glucose, GV seems most detrimental. It can be debated whether GV reflected by MAG change is a causative harmful phenomenon, or whether it is an epiphenomenon, resulting from metabolic deterioration during severe illness and dying.23 We have attempted to elucidate this by excluding patients who were on a withholding care policy and correcting for the maximal SOFA score during admission. From a pathophysiological viewpoint a causal relationship can be substantiated: in vitro, varying glucose levels have been shown to enhance cell apoptosis.24 In rats, glycaemic reperfusion after hypoglycaemia caused neuronal death25 and altering glucose levels were impairing endothelial function in healthy volunteers.26 Even more, tubulointerstitial cells exposed to intermittent high glucose concentrations showed enhanced cell growth and collagen syntheses compared with stable high glucose concentrations.27 Possibly, the adaptive cell mechanisms that are initiated in case of constant hyperglycaemia are
ineffective when the hyperglycaemia is not constant but varying, explaining the toxicity of GV.28

Our findings are in accordance with previous studies that have investigated the relationship between GV and mortality. In the studies of Krinsley and Egi the glucose SD in the ICU was a predictor of mortality, independent of mean glucose10;16 In the study form Bagshaw et al, GV, defined as the occurrence of both hypoglycaemia and hyperglycaemia within 24 hours of ICU admission, was related to ICU mortality. Although these studies reported data from large multicentre cohorts, a strict glycaemic control algorithm was not fully implemented, limiting external validity for the ICU populations treated with strict glycaemic control. Furthermore, Krinsley and Egi used the SD as a measure of variability. Because the blood glucose scale is not normally distributed and asymmetric, he assumptions of parametric statistics do not apply and the SD was therefore not the optimal measure of GV.17 In addition, the SD does not take the change per time into account. Indeed, in our cohort, the MAG change was a stronger predictor of ICU death than SD. Similar results were reported by Dosset et al, who investigated a surgical ICU population and found that the largest absolute change in successive blood glucose measurements during an ICU admission was a strong predictor of ICU death, whereas the SD was not.29

The APACHE II model is the most widely used parameter when correcting for disease severity in GV studies in the ICU.9;10;16 However, the APACHE II model was originally designed to predict mortality in the first 24 hours of ICU admission.21 Indeed we found disease severity to be a confounder with a relation to both glycaemic variability and mortality. Correction for disease severity using maximum SOFA score during admission seemed superior to using APACHE scores at admission.

Our findings suggest that high mean glucose is less harmful when GV is low and patients with identical mean glucose can have different mortality rates, depending on their MAG change. GV was not reported as an outcome measure in the Leuven studies, the GluControl study, the VISEP study and the NICE-SUGAR study.1;2;4;7;8 Differences in these study outcomes may be attributed to several factors.30 It can be hypothesised that more stable glucose profiles, with less GV, can be reached when insulin therapy is combined with a constant administration of glucose-containing fluids, analogous to the insulin clamp technique.31 Because we have found that GV is such a strong predictor of ICU death, there is the possibility that differences in GV can be part of the explanation of differences in mortality reduction in these
Trials. It would be interesting to examine the results of these previous trials in the context of glycaemic variability.

Of note, ICU mortality in the mean glucose quartiles in our study decreased from 10.1% (<6.92 mmol/l) to 3.6% (7.60 to 8.89 mmol/l) and rose hereafter to 7.0% (>8.89 mmol/l). Such a J-shaped mortality curve has been seen before in patients with myocardial infarction and in a large cohort of 66184 ICU patients in whom glucose values during the first 24 hours of admission were taken into account. We cannot explain the increased mortality in the lower glucose quartile solely by the occurrence of severe hypoglycaemia (as defined by glucose ≤2.5 mmol/l). Previous results regarding the relation between severe hypoglycaemia and ICU mortality are conflicting. In our study, the association between ICU mortality in the lowest mean glucose quartile and highest MAG quartile holds after correcting for severe hypoglycaemia in the multivariate analysis. This is in concordance with the study from Bagshaw et al, who found that glucose variability was a stronger predictor of ICU death than hypoglycaemia alone.

An important limitation of this study is that was performed in one centre only and is retrospective in nature. Most patients were admitted for cardiothoracic surgery; we have however corrected for this potential confounder. A strong point is that we studied a large and representative group of 5728 mixed ICU patients who were treated with strict glycaemic control using a computerised algorithm, which brought a high number of patients in target. Furthermore, we used a novel indicator for GV.

**CONCLUSIONS**

We have confirmed findings of previous studies that GV is related to ICU and in-hospital death. Additionally, we have shown that, also for those with persistently high mean glucose values during admission, low GV seems protective. There appears to be a synergistic negative effect of high mean glucose in combination with high GV. To elucidate whether GV is a treatable risk factor in the ICU or a risk marker only, the effect of lowering GV on ICU survival is to be investigated, for example by designing an algorithm which aims at lowering variability rather than the mean glucose and comparing this with an algorithm that lowers the mean glucose.
REFERENCES


Glucose variability is associated with ICU mortality


Chapter 12


Hypoglycaemia is associated with ICU mortality

J Hermanides, RJ Bosman, TM Vriesendorp, R Dotsch, FR Rosendaal, DF Zandstra, JBL Hoekstra, JH DeVries

Critical Care Medicine, In Press
ABSTRACT

Objective The implementation of intensive insulin therapy in the intensive care unit (ICU) is accompanied by an increase in hypoglycaemia. We studied the relation between hypoglycaemia on ICU mortality, since the evidence on this subject is conflicting.

Design Retrospective database cohort study.

Setting An 18-bed medical/surgical ICU in a teaching hospital (Onze Lieve Vrouwe Gasthuis Hospital, Amsterdam, the Netherlands).

Patients 5961 patients admitted to from 2004 to 2007 were analysed. Readmissions and patients with a withholding care policy or with hypoglycaemia on the first glucose measurement were excluded. Patients were treated with a computerised insulin algorithm (target glucose range 4.0 to 7.0 mmol/l).

Measurements All first episodes of hypoglycaemia (glucose <=2.5 mmol/l) were derived from 154015 glucose values. Using Poisson regression, the incidence rates (IR) for ICU death and incidence rate ratio (IRR) comparing exposure and non-exposure to hypoglycaemia were calculated. Patients were considered to be exposed to hypoglycaemia from the event until the end of ICU admittance. We corrected for severity of disease using the daily Sequential Organ Failure Assessment score. Age, sex, cardiothoracic surgery, sepsis and diabetes mellitus were also included as possible confounders.

Main results 288 (4.8%) patients experienced at least one episode of hypoglycaemia. Median age was 68 (58 to 75) years, 66% was male and 6.4% died in the ICU. The IR of death in patients exposed to hypoglycaemia was 40/1000 ICU days, as compared to 17/1000 ICU days in patients without exposure. The adjusted IRR for ICU death was 2.1 (95% CI 1.6-2.8, p<0.001).

Conclusions Hypoglycaemia is related to ICU mortality, also when adjusted for a daily adjudicated measure of disease severity, indicating the possibility of a causal relationship.
INTRODUCTION

Hyperglycaemia in the ICU is common, also in patients without known diabetes, and is related to poor outcome. The implementation of strict glucose control with intensive insulin therapy (IIT) in the Intensive Care Unit (ICU), targeting for a fasting morning glucose of 4.4-6.1 mmol/l was proven to be beneficial with regard to mortality in the two “Leuven” trials, if ICU treatment exceeded five and three days, respectively. Two large multicentre randomised controlled trials were carried out to confirm these results but were terminated prematurely, because of high rates of sever hypoglycaemia or because the target glucose range was not reached. The recently published NICE-SUGAR trial showed that mortality was increased, when the investigators aimed for a blood glucose 4.5 to 6.0 mmol/l in the IIT group as compared to <=10.0 mmol/l in the control group (27.5% vs. 24.9%, p=0.02). Several explanations have already been proposed to explain the conflicting results regarding strict glucose control, including the increased risk of (severe) hypoglycaemia that accompanies IIT. A meta-analysis including the NICE-SUGAR data indicated that IIT was associated with a six-fold increased risk for hypoglycaemic events (95% CI 4.5 to 8.0). However, the causal relation with mortality in the ICU remains unclear. Several studies have specifically investigated outcomes after hypoglycaemia in the ICU and yielded conflicting results. Because it is possible that hypoglycaemia is a risk marker for severe illness or dying, rather than a risk factor for mortality, it is important to correct for severity of disease. All previous studies used the APACHE II score to this purpose, a validated score designed to predict mortality in the first 24 hours of ICU admittance. To discriminate between hypoglycaemia as a risk marker and a risk factor, we reasoned the optimal correction is for severity of disease on the day of the hypoglycaemic event. Therefore in this study we investigated the relation between hypoglycaemia in the ICU and mortality, corrected for a measure of severity of disease taken on the day of the hypoglycaemic event.

MATERIALS AND METHODS

Design and setting
We performed a cohort study in an 18-bed mixed surgical/medical ICU in a teaching hospital (Onze Lieve Vrouwe Gasthuis Hospital, Amsterdam, the Netherlands). The nurse-to-patient ratio was on average 1:2 and all beds were equipped with a clinical information system (iMD-Soft; MetaVision, Tel Aviv,
Glucose regulation protocol
The glucose regulation algorithm (target range 4.0 to 7.0 mmol/l) was fully computerised and connected to the clinical information system. The software suggested an insulin infusion rate based on the current glucose value, the rate of glucose change over the previous 5 measurements, previous insulin drip rates and given insulin boluses. The software also provided the timing of the next glucose measurement which could vary between 15 minutes and 4 hours. In case of a glucose measurement below <3.5 mmol/l the insulin pump was stopped and 20 ml of 30% glucose administered. Glucose was measured 15 minutes hereafter and if euglycaemia was reached, the insulin pump was restarted at 50% of the previous infusion rate. If still below 3.5 mmol/l, glucose was administered again and the insulin pump was not restarted for at least two hours. In case of a glucose measurement between 3.5 and 4.5 mmol/l, the insulin pump infusion rate was decreased with the percentage of decrease between the current and the last glucose value. Within 24 hours after admission, enteral feeding was started, targeting for 2000 kcal/24h within 48 hour or 1500 kcal/24h within 24 hours. In case of gastric retention, a feeding tube was inserted in the duodenum. When normal eating was resumed, the glucose regulation algorithm was stopped. The protocol was implemented in 2001.14

Hypoglycaemia
Glucose was measured from blood samples obtained from an arterial catheter using the AccuCheck (Roche/Hitachi®, Basel, Switzerland). We obtained all measurements from the clinical information system. Hypoglycaemia was defined as one or more glucose measurements <=2.5 mmol/l. This is using the same cut-off value as we used earlier and similar to the cut-off values used by van den Berghe and the NICE-SUGAR investigators (<=2.2 mmol/l).6,13,15 Because the cut-off value for (severe) hypoglycaemia in the ICU in different studies ranges from 2.2 to 4.5 mmol/l, we also assessed the risk for ICU death associated with different cut-off values for hypoglycaemia; <=1.4, 1.9, 3.1, 3.6, 4.2, 4.7, 5.3 and 5.8 mmol/l respectively.
Data collection
All data was extracted from the clinical information system. Patients admitted between January 2004 and January 1st 2008 were included. No changes in the glucose regulation protocol were applied in this period. Readmissions, patients with a withholding care policy and patients who had hypoglycaemia at admission were excluded. We collected information on the medical history, demographic variables and admission diagnosis. For each day of ICU admittance, we calculated the Sequential Organ Failure Assessment (SOFA) Score, as a measure of severity of disease on that particular day. If the SOFA score was not available on the day of ICU discharge, we imputed the SOFA score of the preceding day.

Statistical analyses
Results are presented as median with interquartile range (IQR). We calculated the incidence rate of ICU death per 1000 ICU days for patients with- and without hypoglycaemia and calculated the crude incidence rate ratio (IRR), thereby assuming a more or less constant hazard for ICU death. Every calendar day of ICU admittance was counted as 1 day of ICU admittance. When a patient experienced hypoglycaemia, we considered the patient to be exposed all subsequent days of the ICU admittance. To correct for severity of disease per day, we divided the daily SOFA scores into tertiles and compared mortality in the exposed to the non-exposed within each SOFA tertile. We created tertiles to maintain sufficient power for multivariate analyses. Using Poisson regression, we adjusted the IRR for the altering SOFA-tertile. We also included the interaction between SOFA-tertile and ICU admission days in the model (SOFA tertile*ICU admission days), as the predictive value of the SOFA score differs when patients are admitted longer. Furthermore, we adjusted for admission diagnosis of sepsis, according to the APACHE II diagnostic criteria, as this can cause hypoglycaemia and is also related to ICU mortality. Diabetes mellitus is known to predispose patients to hypoglycaemia in the ICU however might affect outcome positively and was therefore included in the analyses. Cardiac surgery was also included as a potential confounder, because mortality among cardiothoracic patients is generally lower and they differ with respect to several demographic and physiological characteristics.

Finally, the analyses were adjusted for age and sex. The same analysis was performed for different cut-off values for hypoglycaemia. All statistical analyses were performed in SPSS 16.0 (SPSS Inc., Chicago, IL, USA).
RESULTS

From 6725 admissions, 5961 patients were eligible for analyses after excluding 656 readmissions and patients with a withholding care policy (n=86) or glucose <=2.5 mmol/l according to their first glucose measurement (n=22). The patient characteristics are displayed in Table 1 and Table 2. In total 154015 glucose values were collected, a median of 11 values per day per patient (IQR 6 to 14). Median age was 68 years (IQR 58 to 75), 66% of the population was male and 6.4% of the patients died in the ICU. Patients were in target range a median of 42% of the time (IQR 17 to 56) and 288 (4.8%) of patients encountered one or more episodes of hypoglycaemia (<=2.5 mmol/l) and of these 113 patients experienced more than 1 episode. In total we collected 20737 SOFA scores (1152 missing scores (5.6%), mainly SOFA scores of discharge day), of which the tertiles ranged from 0-4, 5-6, >6.
Hypoglycaemia is associated with ICU mortality

<table>
<thead>
<tr>
<th>Age, years (median, IQR)</th>
<th>Surgical (n=4582)</th>
<th>Medical (n=1379)</th>
<th>Total cohort (n=5961)</th>
</tr>
</thead>
<tbody>
<tr>
<td>68 (59 to 78)</td>
<td>64 (52 to 76)</td>
<td>68 (58 to 75)</td>
<td></td>
</tr>
<tr>
<td>Gender, male n (%)</td>
<td>3058 (67)</td>
<td>863 (62)</td>
<td>3907 (66)</td>
</tr>
<tr>
<td>APACHE II score on admission (median, IQR)</td>
<td>15 (12 to 17)</td>
<td>24 (18 to 31)</td>
<td>16 (13 to 20)</td>
</tr>
<tr>
<td>Max SOFA score during admission* (median, IQR)</td>
<td>5 (4 to 6)</td>
<td>8 (5 to 11)</td>
<td>6 (4 to 7)</td>
</tr>
<tr>
<td>ICU stay, days (median (IQR)</td>
<td>0.9 (0.8 to 1.1)</td>
<td>2.6 (1.1 to 5.3)</td>
<td>1.0 (0.8 to 2.0)</td>
</tr>
<tr>
<td>Diabetes mellitus, n (%)</td>
<td>691 (15.1)</td>
<td>8 (0.6)</td>
<td>699 (11.7%)</td>
</tr>
<tr>
<td>Died ICU, n (%)</td>
<td>81 (1.8)</td>
<td>305 (21.8)</td>
<td>380 (6.4%)</td>
</tr>
<tr>
<td>Died hospital, n (%)</td>
<td>211 (4.6)</td>
<td>445 (31.9)</td>
<td>648 (10.9%)</td>
</tr>
<tr>
<td>Severe hypoglycaemia (&gt;= 1 event), n (%)</td>
<td>111 (2.4)</td>
<td>177 (12.8)</td>
<td>288 (4.8%)</td>
</tr>
<tr>
<td>Admission Category n (%)</td>
<td>4012 (87.6)</td>
<td>253 (18.3)</td>
<td>4265 (71.5)</td>
</tr>
<tr>
<td>-Cardiovascular</td>
<td>10 (0.2)</td>
<td>298 (21.6)</td>
<td>308 (5.2)</td>
</tr>
<tr>
<td>-After cardiac arrest</td>
<td>53 (1.2)</td>
<td>221 (16.0)</td>
<td>274 (4.6)</td>
</tr>
<tr>
<td>-Gastrointestinal</td>
<td>255 (5.6)</td>
<td>57 (4.1)</td>
<td>312 (5.2)</td>
</tr>
<tr>
<td>-Haematological</td>
<td>8 (0.2)</td>
<td>9 (0.7)</td>
<td>17 (0.3)</td>
</tr>
<tr>
<td>-Renal</td>
<td>12 (0.3)</td>
<td>26 (1.9)</td>
<td>38 (0.6)</td>
</tr>
<tr>
<td>-Metabolic</td>
<td>7 (0.2)</td>
<td>45 (3.3)</td>
<td>52 (0.9)</td>
</tr>
<tr>
<td>-Neurological</td>
<td>47 (1.0)</td>
<td>168 (12.2)</td>
<td>215 (3.6)</td>
</tr>
<tr>
<td>-Respiratory</td>
<td>178 (3.9)</td>
<td>302 (21.9)</td>
<td>476 (8.0)</td>
</tr>
</tbody>
</table>

Table 1 - population characteristics; APACHE Acute Physiology and Chronic Health Evaluation, SOFA Sequential Organ Failure Assessment ICU Intensive Care Unit *Maximum score of the total scores calculated each ICU day

<table>
<thead>
<tr>
<th>No severe hypoglycaemic episode (n=5673)</th>
<th>&gt;=1 severe hypoglycaemic episode (n=288)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years (median, IQR)</td>
<td>68 (58 to 75)</td>
</tr>
<tr>
<td>Gender, male n (%)</td>
<td>3740 (65.9)</td>
</tr>
<tr>
<td>APACHE II score on admission (median, IQR)</td>
<td>15 (12 to 19)</td>
</tr>
<tr>
<td>SOFA score* (median, IQR)</td>
<td>5 (4-7)</td>
</tr>
<tr>
<td>ICU stay, days (median (IQR)</td>
<td>1.0 (0.8 to 1.9)</td>
</tr>
<tr>
<td>Diabetes mellitus, n (%)</td>
<td>666 (11.7)</td>
</tr>
<tr>
<td>Died ICU, n (%)</td>
<td>312 (5.5)</td>
</tr>
<tr>
<td>Died hospital, n (%)</td>
<td>549 (9.7)</td>
</tr>
<tr>
<td>Medical admission, n (%)</td>
<td>1202 (21.2)</td>
</tr>
<tr>
<td>Surgical admission, n (%)</td>
<td>4471 (78.8)</td>
</tr>
</tbody>
</table>

Table 2 - population characteristics for patients with- and without severe hypoglycaemia; APACHE Acute Physiology and Chronic Health Evaluation, SOFA Sequential Organ Failure Assessment ICU Intensive Care Unit *Maximum score during admission, calculated from the total scores calculated each ICU day
ICU mortality and hypoglycaemia

The IR of ICU death was 19/1000 ICU days. The overall IR for ICU death after experiencing a hypoglycaemic event was 40/1000 ICU days, as compared to 17/1000 ICU days without a hypoglycaemic episode, crude IRR 2.3 (95% CI 1.8 to 3.1, p<0.001). The IRs after experiencing hypoglycaemia were higher across all SOFA score ranges (Figure 1). After adjusting for age, sex, admission for cardiothoracic surgery, sepsis, SOFA score, ICU days and the interaction between SOFA score and ICU days, the adjusted IRR was to 2.1 (95% CI 1.6 to 2.8, p<0.001). The crude IR for patients experiencing only one episode of hypoglycaemia was 36/1000 ICU days as compared to 42/1000 ICU days for patients with more than one episode, IRR 1.2 (95% CI 0.7 to 2.0, p=0.58). When the APACHE II score was used to correct for severity of disease, instead of the daily SOFA score, the IRR for ICU death was 1.6 (95% CI 1.2 to 2.1).

Figure 1- the incidence of intensive care unit (ICU) death per 1000 ICU days with and without hypoglycaemia (<=2.5 mmol/l) for daily sequential organ failure scores (SOFA) 0 to 4, 5 to 6 and >6.
Figure 2 shows the adjusted IRRs for the different cut-off values for hypoglycaemia in the ICU. There was an increased risk for ICU death up to the cut-off value of 4.7 mmol/l, IRR 1.4 (95% CI 1.1 to 1.8, \( p=0.006 \)). With cut-off values above 4.7 mmol/l, no effect on IRR for ICU death was found, IRR 1.1 (0.9 to 1.4, \( p=0.44 \)).

**DISCUSSION**

In this cohort study we showed that hypoglycaemia (\( \leq 2.5 \) mmol/l) in the ICU is accompanied by an increase in ICU death 2.1 (95% CI 1.6 to 2.8, \( p<0.001 \)) after adjusting for the daily SOFA score over time.

In a previous nested case-control study we did not find an association between hypoglycaemia and in-hospital death (hazard ratio 1.03, 95% CI 0.68 to 1.56) in a relative small sample of 156 hypoglycaemic events.\(^{13}\) Arabi and coworkers also found no significant relation between hypoglycaemia and ICU mortality.\(^{12}\) In contrast with these findings, Krinsley et al. found in a small retrospective case-control designed study that hypoglycaemia (\(< 2.2 \) mmol/l) was associated with an increased mortality risk (OR 2.28, 95% CI 1.41 to 3.70) in a population that was only partly treated with IIT.\(^{11}\) Also, Bagshaw et al showed in a large multicentre ICU cohort (n=66,184), that the OR for ICU mortality after exposure to a glucose
value <4.5 mmol/l was 1.41 (95% CI 1.31 to 1.54). However, this study was limited to the first 24 hours of ICU admission and a relative small number of glucose values per patient (~2) were collected.

All previous studies used the APACHE II score to correct for disease severity. We excluded patients with a severe hypoglycaemia as the first glucose measurement. This was because these patients were not under strict glucose control before the event and spontaneous hypoglycaemia can be a marker of severe disease.

A strength of the current study is that we attempted to adjust for severity of disease as a changing variable over time in stead of using the APACHE II score. Although APACHE II is validated to predict mortality, it is determined at ICU admission and does not take any changes thereafter into account. The SOFA score is a measure of disease severity that it is updated daily during admittance and therefore seems to provide a better distinction between hypoglycaemia as a risk factor or risk marker. The use of the SOFA score is limited by the interaction with time spent in the ICU and different predictive power of identical SOFA scores depending on the failing organ systems that contribute to the score. However, in the current study it was the best available predictive score that could be assessed on a daily basis and it is validated to discriminate between ICU survivors and non-survivors. Furthermore, we have attempted to correct for the interaction with time spent in ICU by including this in the model. After experiencing a hypoglycaemic event, we considered patients to be exposed the remaining days of the ICU admittance, because from a pathophysiological viewpoint hypoglycaemia may cause damage that is, at least during ICU stay, likely to be sustained.

Hypoglycaemia may contribute to ICU mortality by inducing neuroglycopenia with neuronal cell loss and hypoglycaemic coma, especially after hyperglycaemic reperfusion. Furthermore, hypoglycaemia might provoke ischemia in pre-existing vascular disease in diabetic patients and it has also been shown to induce platelet activation and inflammation in experimental setting. Hypoglycaemia could thus contribute to ICU mortality by aggravating overall illness.

Another strength of this study is that adequate glycaemic control was achieved while the hypoglycaemia rate was low compared to other studies. Our study is limited by its single-centre origin. However, there was a high quality of data collection, because all clinical information and laboratory values were directly or even automatically stored in the computerised clinical information system.

The additional analyses we performed investigating different cut-off values for hypoglycaemia showed that up to 4.7 mmol/l, hypoglycaemia was associated with a
significant increased risk for ICU death. This is in concordance with the study of Bagshaw and colleagues, who found an increased mortality risk when defining hypoglycaemia as <4.5 mmol/l. The recently published NICE-SUGAR study was the start of a debate about the optimal blood glucose range in the ICU and a higher, perhaps safer range than the tight range of the Leuven studies is proposed. The present and previous studies thus suggest that hypoglycaemia might be harmful when aiming for strict glycaemic control, targeting for a range between 4.0 to 7.0 mmol/l.

Future investigations looking at strict glycaemic control in the ICU should consider the possibility that even glucose values below 4.7 mmol/l are harmful. Higher target ranges for glucose control will diminish the incidence hypoglycaemia and seem justified.

CONCLUSIONS

Hypoglycaemia is related to ICU mortality, also when adjusted for a daily adjudicated measure of disease severity. Although residual confounding can never be ruled out, a causal relationship between hypoglycaemia and ICU mortality is a likely possibility.
REFERENCES


Hypoglycaemia is associated with ICU mortality


(26) Suh SW, Gum ET, Hamby AM, Chan PH, Swanson RA. Hypoglycemic neuronal death is triggered by glucose reperfusion and activation of neuronal NADPH oxidase. JAMA 2009; 301(15):1556-1564.


Mean glucose during ICU admission is related to mortality by a U-shaped curve; implications for clinical care

SE Siegelaar, J Hermanides, HM Oudemans- van Straaten, PHJ van der Voort, RJ Bosman, DF Zandstra, JH DeVries

Submitted for publication
ABSTRACT

Purpose To determine in which way glucose regulation is associated with ICU mortality thereby trying to reconcile the conflicting data from the Leuven and NICE-SUGAR trials, since recently the optimal glucose target range has become unclear.

Methods Retrospective database cohort study including patients admitted between January 2004 and December 2007 in a 20-bed medical/surgical ICU in a teaching hospital. Hyperglycaemia was treated using a fully computerised algorithm targeting for glucose levels of 4.0 to 7.0 mmol/l. 5983 patients were eligible for analyses. We randomly selected 2435 patients with a surgical/medical ICU admission ratio of 55/45%, to enable comparison with the Leuven and NICE-SUGAR populations.

Results The cohort was subdivided in deciles of increasing mean glucose. We examined the relation between mean glucose strata and mortality. We observed the highest mortality in the lower and higher strata. Logistic regression analysis adjusted for age, sex, APACHE II score and admission duration showed that mean glucose levels <7.0 mmol/l and >9.0 mmol/l were associated with significantly increased ICU mortality (OR >=2.06 and >=2.33 respectively). Limitations of the study were its retrospective design and possible incomplete correction for severity of disease.

Conclusions Mean glucose during ICU admission is related to mortality by a U-shaped curve. A ‘safe range’ of mean glucose regulation might be defined between 7.0 and 9.0 mmol/l. The U-shaped curve may help to explain the increased mortality in the intensively treated group of the NICE-SUGAR study but is at odds with the low mortality in the intensively treated groups of the Leuven studies.
INTRODUCTION

Due to inflammatory and neuro-endocrine derangements in critically ill patients, stress hyperglycaemia associated with high hepatic glucose output and insulin resistance is common in the intensive care unit (ICU).\(^1\) This stress hyperglycaemia is associated with poor outcome.\(^2\) Moreover, several studies report a deleterious effect of glycaemic variability over and above mean glucose, after correction for severity of disease.\(^3\)-\(^5\)

In 2001 van den Berghe and colleagues published the first randomised controlled trial (RCT) comparing normalization of glycaemia by intensive insulin treatment (IIT) with conventional glycaemic control at a surgical ICU (glucose target: 4.4 to 6.1 mmol/l versus 10.0 to 11.1 mmol/l).\(^6\) They reported an impressive reduction in mortality with IIT. This same group failed to reproduce these findings in the entire population of patients in their medical ICU,\(^7\) however mortality was lower in the predefined subgroup of patients receiving IIT for more than three days. After pooling of the data of both RCT's IIT seemed associated with a reduction in mortality.\(^8\) Based on these 'Leuven trials', many hospitals decided to implement protocols and target normalisation of glucose levels to improve patient care.

Recently, after the publication of two inconclusive multicentre studies (the Volume Substitution and Insulin Therapy in Severe Sepsis [VISEP]\(^9\) and the GluControl\(^10;11\) studies) followed by the very recently reported Normoglycaemia in Intensive Care Evaluation- Survival Using Glucose Algorithm Regulation (NICE-SUGAR) trial\(^12\), confusion has been raised about the optimal tightness of control: the NICE-SUGAR trial investigators reported an absolute increase in deaths at 90 days with IIT (glucose target: 4.5 to 6.0 mmol/l versus 8.0 to 10.0 mmol/l). Additionally, a recently published meta-analysis including this latter trial showed that intensive insulin therapy significantly increased the risk of hypoglycaemia and conferred no overall mortality benefit among critically ill patients.\(^13\)

The goal of this study is to report glucose and mortality data from a general ICU of a teaching hospital in the Netherlands and to compare these data with the results of the Leuven studies and NICE-SUGAR trial, with the goal to come to terms regarding the cause of their conflicting results and to define the optimal tightness of glycaemic control.
MATERIALS AND METHODS

Cohorts, setting and data collection
We collected information about patients admitted between January 2004 and December 2007 in a 20-bed medical/surgical ICU in a teaching hospital (Onze Lieve Vrouwe Gasthuis Hospital, Amsterdam, the Netherlands; the OLVG cohort). The average patient-to-nurse ratio was 1:2. All beds were equipped with a clinical information system (iMD-Soft; MetaVision, Tel Aviv, Israel) from which all clinical and laboratory data was extracted. The glucose regulation algorithm was implemented successfully in 2001\textsuperscript{14}, targeting for glucose values between 4.0 and 7.0 mmol/l. Using a sliding scale computerised algorithm, the nursing staff was instructed to adjust the insulin infusion rate depending on the current glucose value and the rate of glucose change (based on the previous five measurements). The software also provided the time the next glucose measurement was due, which could vary from 15 minutes up to 4 hours. Routinely, enteral feeding was started within 24 hours after admission, aiming at 1500 ml within 24 hours, and subsequently adjusted to the patient’s requirements. A duodenal feeding tube was inserted in case of persistent gastric retention. The tight glucose algorithm was deactivated when patients resumed normal eating.

We excluded readmissions, patients with a withholding care policy and patients with only one glucose value measured during admission. From these patients we randomly allocated a definitive population in which 45% of the patients had a medical ICU admission diagnosis and 55% of the patients a surgical ICU admission diagnosis. This ratio lies in between the populations of the Leuven and NICE-SUGAR studies. From the clinical information system we collected demographic variables, mortality rates in the ICU and glucose values. As severity of disease measures we used the maximal Sequential Organ Failure Assessment (SOFA) score, which was determined daily during ICU admission\textsuperscript{15} and the Acute Physiology and Chronic Health Evaluation II (APACHE II) score\textsuperscript{16}. Informed consent is not required according to Dutch Ethical Review Board regulations, because a retrospective analysis of anonymous data was performed.

Glucose measurers
For each patient we calculated the mean overall glucose during admission from all glucose values measured during admission and the mean morning glucose from the first value available between 5.00h and 7.00h am per patient per day. Glucose was obtained from arterial blood samples, with a handheld glucose measurement device.
Mean glucose in the ICU is related to mortality by a U-shaped curve

(AccuCheck, Roche/Hitachi®, Basel, Switzerland). Results were automatically stored in the clinical information system.

For comparison with the combined Leuven and NICE-SUGAR studies, we used the mean glucose during admission and ICU mortality rates as published for both the IIT and conventional group.

Data interpretation
The cohort characteristics are presented as mean ± standard deviation (SD) or median with interquartile range (IQR), depending on the distribution of the data. The mean glucose values and standard deviations were divided into 10 strata with equal numbers of patients per group. For each stratum, the ICU mortality was calculated. Subsequently we performed a logistic regression analysis to calculate the odds ratio (OR) for ICU mortality per glucose stratum. The stratum with the lowest mortality incidence was used as reference. In this model we adjusted for age, sex, severity of disease (APACHE II score) and admission duration (i.e. <= or >24hr). The latter because glucose values are higher and have a wider range in the first 24 hours of admission, biasing the patients with longer admission times and corresponding lower mean glucose values. For the combined Leuven studies and the NICE-SUGAR study, we assessed the 95% population range around the mean glucose by taking the mean minus- and plus 1.96 times the standard deviation. We plotted the mortality rate in the Leuven and NICE-SUGAR trials against the mortality in the corresponding stratum of mean glucose in our cohort.

RESULTS

In total 5983 patients were eligible for analyses of the mean glucose for the OLVG population after excluding 656 readmissions, 86 patients with a withholding care policy and 155 patients with only one glucose value measured. From this population we randomly selected the final cohort of 2435 patients with a surgical/medical ICU admission ratio of 55/45%, to enable comparison with the Leuven and NICE-SUGAR populations. In the final cohort a median (IQR) of 12 (8 to 14) glucose values per admission day per patient was collected. The total population and the random sample are comparable regarding all baseline characteristics (data not shown). The characteristics of our population and those in the Leuven and NICE-SUGAR trials are displayed in Table 1.
Mean glucose

The overall mean (SD) glucose of the OLVG population was 8.0 (2.3) mmol/l (Table 1). The mean glucose values of the first 24 hours of admission were larger and had a wider range than mean glucose values after 24 hours (mean [SD] 8.3 [2.8] mmol/l, range 0.6 to 40.2 mmol/l and 7.2 [1.6] mmol/l, range 3.2 to 31.1 mmol/l respectively). The mean morning glucose was 7.5 [2.5] mmol/l.

After dividing the mean glucose into ten equally sized strata, the lowest mean glucose stratum ranged 6.3 mmol/l and below. The highest stratum went up from 10.3 mmol/l. Mean glucose ranges per stratum and corresponding mortality rates are displayed in Figure 1. This results in a U-shaped curve relation between glucose and mortality, with high mortality in the lowest and highest glucose-stratum, 21.3% and 27.6% respectively. The strata of the total population showed a comparable U-curve with the random sample (data not shown). Logistic regression analysis showed that glucose values below 7.0 mmol/l and above 9.1 mmol/l were associated with a significant higher OR for ICU mortality compared to the stratum with the lowest mortality (stratum 6). This results in a ‘safe range’ of 7.0 up to 9.0 mmol/l (Figure 2). The mean glucose, SD and 95% population range of the combined Leuven and NICE-SUGAR studies are depicted in Table 1.

In the NICE-SUGAR study, the mean glucose of the IIT group (6.4 mmol/l) falls into the stratum with increased mortality compared to the conventional group (8.0 mmol/l), which lies in the safe range of the OLVG population (Figure 1). The mean of the IIT group of the combined Leuven studies (5.8 mmol/l) falls into the stratum of 6.3 mmol/l and below, where mortality in the OLVG cohort is highest. The mean of the conventional group in the combined Leuven studies (8.4 mmol/l) lies in the safe range of the OLVG population (Figure 1).
Table 1 - Characteristics of the studied cohorts. Hypoglycaemia was defined as at least one glucose value $\leq 2.2$ mmol/l. Time-weighted blood glucose for IIT, Intensive Insulin Therapy; APACHE, Acute Physiology and Chronic Health Evaluation; SOFA, Sequential Organ Failure Assessment; ICU, Intensive Care Unit; n.a.; not available.

<table>
<thead>
<tr>
<th></th>
<th>NICE-SUGAR IIT (n=2435)</th>
<th>Conventional (n=1388)</th>
<th>NICE-SUGAR IIT (n=1360)</th>
<th>Conventional (n=3014)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years (mean ± SD)</td>
<td>63.9 ± 15.1</td>
<td>63 ± 15</td>
<td>63 ± 15</td>
<td>60 ± 17</td>
</tr>
<tr>
<td>Gender, female n (%)</td>
<td>857 (35.2)</td>
<td>460 (34)</td>
<td>449 (32)</td>
<td>1128 (37)</td>
</tr>
<tr>
<td>Diagnostic group, n (%)</td>
<td>1096 (45)</td>
<td>765 (55)</td>
<td>783 (58)</td>
<td>1121 (37)</td>
</tr>
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<td>APACHE II score on admission (mean ± SD)</td>
<td>20.3 ± 8.6</td>
<td>22.5 (16.2)</td>
<td>25.7 ± 9.9</td>
<td>20.1 (15.4)</td>
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<td>Diabetes Mellitus, n (%)</td>
<td>180 (7.4)</td>
<td>207 (15)</td>
<td>200 (14)</td>
<td>615 (20)</td>
</tr>
<tr>
<td>BMI (mean ± SD)</td>
<td>27.2 ± 20.7</td>
<td>25.7 ± 4.9</td>
<td>27.9 ± 7.7</td>
<td>28.0 ± 7.2</td>
</tr>
<tr>
<td>Died ICU, n (%)</td>
<td>302 (12.4)</td>
<td>179 (13.2)</td>
<td>225 (16.2)</td>
<td>546 (18.1)</td>
</tr>
<tr>
<td>Morning glucose, mmol/l (mean ± SD)</td>
<td>7.5 (2.5)</td>
<td>n.a.</td>
<td>n.a.</td>
<td>6.5 (1.4)</td>
</tr>
<tr>
<td>Overall glucose, mmol/l (mean ± SD)</td>
<td>8.0 (2.3)</td>
<td>5.8 (1.3)</td>
<td>8.4 (1.3)</td>
<td>6.4 (1.0)</td>
</tr>
</tbody>
</table>

Hypoglycaemia incidence (%) |
55% population range (mmol/l) |
Overall glucose, mmol/l (mean ± SD) |
Morning glucose, mmol/l (mean ± SD) |
BMI (mean ± SD) |
Diabetes Mellitus, n (%) |
APACHE II score on admission (mean ± SD) |
Gender, female n (%) |
Aged, year (mean ± SD) |

*Mean glucose in the ICU is related to mortality by a U-shaped curve*
**Figure 1** - ICU mortality per mean glucose stratum with the highest mortality in the lowest and highest strata. The mean glucose values and ICU mortality data of the Leuven and NICE-SUGAR IIT and C groups are plotted in the graph. ICU, Intensive Care Unit; SD, standard deviation; IIT, intensive insulin treatment; C, conventional treatment.

**Figure 2** - Odds ratio (OR) for mortality per glucose stratum with the highest OR in the lowest and highest strata. Logistic regression model adjusted for age, sex, APACHE II score and admission duration (≤ and > 24hr). *p<0.05, **p<0.001. ICU, Intensive Care Unit.
Hypoglycaemia
In total 161 (6.6%) patients of this cohort suffered from at least 1 hypoglycaemic episode during ICU admission, defined as a glucose value \( \leq 2.2 \text{ mmol/l} \). 17.9% of all deaths during ICU admission concerned patients who had experienced hypoglycaemia. Regarding the lowest mean glucose stratum (mean glucose \( \leq 6.3 \text{ mmol/l} \)), 34.6% of the patients that died at the ICU had experienced a hypoglycaemic episode and 65.4% did not. The incidence of hypoglycaemia in the different the mean glucose and variability cohorts is reported in Figure 3.

**Figure 3** - Hypoglycaemia incidence per mean glucose stratum

DISCUSSION
Mean glucose values between 7.0 and 9.0 mmol/l during ICU stay are associated with the lowest OR for mortality at the ICU, while mean values below 7.0 and higher than 9.0 mmol/l confer significantly higher OR’s. These results were attained while using a glucose algorithm that targeted for glucose values between 4.0 and 7.0 mmol/l. The finding that hyperglycaemia is associated with increased mortality is in accordance with published literature.\(^2\) Also, the U-shaped curve we found, with increased mortality in the lower and upper quadrants, is described earlier in patients with myocardial infarction during admission\(^{17-19}\), in the ICU setting for the first 24 hours of admission\(^{20}\) and more generally in patients with type 2 diabetes mellitus\(^{21}\), corroborating this finding.
Hypoglycaemia seems to be associated with increased mortality at the ICU. In our population the incidence of hypoglycaemia was highest in the lowest mean glucose cohorts in which mortality was higher as well. In addition, a significant part of the patients who died had experienced a hypoglycaemic episode. However, hypoglycaemia can only partially account for the considerable mortality rate in the lowest mean glucose stratum since 65.4% of the non-survivors did not experience hypoglycaemia. However, it might be possible that some hypoglycaemic episodes were not recorded due to intermittent sampling or were underestimated due to the AccuChek point-of-care meter used for glucose measurements, results of which tend to be higher than those obtained from the laboratory. Also, low blood sugars are perhaps already harmful above the current cut-off value of 2.2 mmol/l. Therefore the contribution of hypoglycaemia to ICU death could be underestimated and needs further research using continuous glucose measurement.

We plotted the reported NICE-SUGAR and combined Leuven mean glucose data in Figure 1. This shows that the findings of the NICE-SUGAR trial are in accordance with the mortality data from our cohort; the mean glucose of their IIT group is according to our data also associated with a higher ICU mortality rate than the conventionally treated group. This is in contrast with data of the combined Leuven studies (Figure 1). According to our U-curve the mean glucose value achieved in the combined Leuven conventionally treated group would correspond with a lower mortality rate than the mean glucose achieved in their intensively treated group, which is opposed to their findings. Since the mean mortality and mean glucose values of the conventionally treated groups of both the combined Leuven and NICE-SUGAR studies are roughly comparable, it seems that the mortality rate of the combined Leuven IIT group is lower than expected. A possible explanation for the low mortality of the Leuven IIT group might be lower glucose variability. In addition to hypoglycaemia, glycaemic swings are a known risk factor of ICU death. Also after an attempt for correction using severity of disease measures glucose variability remains an independent predictor of mortality in the OLVG population. In addition, other explanations have been proposed to explain the diverging outcomes of Leuven and NICE-SUGAR.

Baseline characteristics from our sample and the combined Leuven and NICE-SUGAR studies were reasonably comparable, only the proportion of patients with diabetes mellitus in our sample is smaller, 7.4% versus 14.5 and 20.0% in the combined Leuven and NICE-SUGAR studies respectively). This may be due to a difference in definition since in our population diabetes mellitus was only scored when the patient used anti-hyperglycaemic drugs, probably leading to an
underestimation of the proportion of patients with diabetes mellitus in our population. The APACHE II score at admission was lower in the Leuven studies, which might be due to a larger proportion of (cardiothoracic) surgery patients, of whom on average APACHE II score and mortality rate were lower than in medical patients.\textsuperscript{6,7}

The mean glucose of the OLVG population (8.0 mmol/l) was higher than the target range, between 4.0 and 7.0 mmol/l. Other studies of intensive insulin therapy also did not reach their target range, illustrating the difficult implementation of this therapy.\textsuperscript{9,11,12} Also short ICU admission duration in the OLVG population makes it more difficult to reach the glucose target because glucose values are higher and have a wider range in the first 24 hours of admission (median duration of stay 1.5 days in our cohort compared to 3 days in the Leuven cohort and 4.2 days 'on algorithm' in the NICE-SUGAR study). Furthermore, our patients were treated in a normal-care setting without the extra stimuli of a trial setting to achieve the target. Mean glucose does not equal time in target range, as the protocol requires more frequent sampling when not in target, thus falsely inflating the mean.

The rate of hypoglycaemia in our population was comparable with the NICE-SUGAR study intensively treated group despite a higher mean glucose in our population. Lack of a study effect and perhaps a different sampling frequency might also have contributed to this observation\textsuperscript{30}. Moreover, patients with a medical admission diagnosis experience more hypoglycaemic events.\textsuperscript{25} Taking that into account, other studies implementing intensive insulin therapy observed comparable rates of severe hypoglycaemia in their intensively treated groups compared to our population.\textsuperscript{9,11}

In our logistic regression model we adjusted for severity of disease and admission duration less or more than 24 hours, since both high and low glucose levels could be a manifestation of severe disease rather than a cause. Glucose values are higher and have a wider range in the first 24 hours of admission, biasing the patients with longer admission times and corresponding lower mean glucose values. A limitation of our correction for severity of disease is the use of the APACHE II score, because the use of APACHE II to predict mortality is not validated for cardiothoracic surgery patients. However, this adjustment is the best available method.\textsuperscript{31}

**CONCLUSIONS**

According to our data the mean glucose during ICU stay is related to mortality by a U-shaped curve; a ‘safe range’ for mean glucose can be defined between 7.0 and 9.0 mmol/l, while both higher and lower mean values are associated with higher
mortality. Secondly, comparison of the combined Leuven, NICE SUGAR and our cohorts learns that the increased mortality in the IIT group of NICE-SUGAR is in line with our U-shaped curve. Low glucose variability may have contributed to their corresponding low mortality. According to these findings and awaiting further studies we recommend treating hyperglycaemia at the ICU in a moderately intensive way, targeting for mean glucose values between 7.0 and 9.0 mmol/l and avoiding hypoglycaemia. This ‘safe range’ should be studied prospectively in randomised clinical trials.
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Mean glucose in the ICU is related to mortality by a U-shaped curve


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Summary and future considerations
Samenvatting en toekomstperspectief
List of Publications
Biografie
Co-authors
Dankwoord

J Hermanides
Summary and future considerations
What are the consequences of hyperglycaemia, how do we measure it and what measures do we need to take? These questions were the base of this thesis. In PART I, the consequences of hyperglycaemia are investigated in relation to the coagulation system and thromboembolism. We especially focused on the effects of acute hyperglycaemia resulting from surgery in patients with and without diabetes mellitus. PART II of the thesis is about the detection and treatment of hyperglycaemia. The sensor augmented pump therapy as a new detection and treatment tool is the subject of several chapters. The final chapters concern the treatment of hyperglycaemia in the Intensive Care Unit (ICU).

PART I

Chapter 2 gives an overview of the current evidence of the role of hyperglycaemia in activating the coagulation system. Evidence is mounting that both chronic and acute hyperglycaemia contribute to coagulation activation and hypofibrinolysis, resulting in a procoagulant state that predisposes patients to thrombotic events. Intensive glycaemic control in patients with diabetes mellitus reduces the incidence of thrombotic diseases such as myocardial infarction and stroke. Whether intensive glucose control during acute hyperglycaemia will be beneficial needs further investigation in randomised controlled trials.

Chapter 3 confirms the association between hyperglycaemia and coagulation: a cohort of consecutive patients referred for suspected deep vein thrombosis was investigated. 188 cases with confirmed venous thromboembolism (VTE) were compared to 370 controls. Increased glucose levels at presentation in the outpatient clinic were associated with increased odds ratios for actually having VTE. This is the first report on this association and now confirmation in other studies is required.

In Chapter 4 the effect of hip surgery on glucose metabolism and coagulation activation was studied in 9 patients without diabetes mellitus undergoing elective hip surgery. Hip surgery clearly induced a rise in glucose levels, which preceded a proportional rise of factor VIII clotting activity, von Willebrand ristocetin cofactor activity, von Willebrand factor antigen and prothrombin fragment 1+2. These results suggests a possible role of hyperglycaemia in activating the coagulation system.
Chapter 5 supports the suggestion we made in chapter 4: increased glucose levels after elective hip surgery were predictive of later development of venous thromboembolism. We performed post-hoc analyses of four previously performed studies investigating patients undergoing total hip or knee replacement. Our outcome measures were symptomatic VTE and “total VTE” (defined as the composite of symptomatic VTE, asymptomatic DVT and all cause mortality). We analysed 12383 patients who underwent elective hip- and knee-surgery. Postoperative glucose levels measured at day 1 were associated with total VTE in patients undergoing hip surgery. Also, the increase of glucose levels during hip surgery was associated with the development of symptomatic and total VTE. This was not demonstrated in patients undergoing total knee replacement, which is likely due to the surgical procedure. This indicates that hyperglycaemia develops as a consequence of hip surgery and contributes to the development of post-surgical VTE.

In Chapter 6 a different patient group was studied: 330 consecutive patients undergoing pancreatoduodenectomy. Glucose was measured before-, during-, and after surgery. In concordance with previous studies, early postoperative hyperglycaemia was induced by the procedure and appears to be a strong predictor of postoperative complications.

All of the previous studies show that acute hyperglycaemia occurs even without known diabetes preictipated by a pathophysiological stressor, such as surgery or illness. Postoperative hyperglycaemia is associated with VTE after hip surgery and with complications after pancreatodoudenectomy. Future studies should focus on preventing the development of perioperative hyperglycaemia and study the effect in randomised controlled setting. As intensive insulin therapy can be time consuming and carries the risk of hypoglycaemia, the use other glucose lowering agents should be considered, such as oral antidiabetics or GLP-1 analogs.

PART II

Chapter 7 provides a view on the current evidence of the clinical application of subcutaneous glucose sensors (CGM), alone or combined with subcutaneous insulin pumps. In several studies, CGM lowered HbA1c in adult patients with poorly controlled type 1 diabetes mellitus, when selecting compliant patients who tolerate the device. However, as a preventive tool for hypoglycaemia, CGM is not yet
effective. Increasing reimbursement of CGM is expected in the near future and studies on cost-effectiveness are awaited.

**Chapter 8** describes the EURYTHMICS trial (EURopean trial (Y) To lower HbA$_{1c}$ by Means of an Insulin pump augmented by a Continuous glucose Sensor). In a randomised controlled trial in 8 European countries, the efficacy of sensor augmented pump therapy was investigated in 83 patients with type 1 diabetes mellitus and HbA$_{1c}$ $\geq$ 8.2%. Patients were randomised to either sensor augmented pump with mealtime bolus advisor for 26 weeks or to the control group using multiple daily injection therapy. We showed that sensor augmented pump therapy effectively lowered HbA$_{1c}$ by 1.21% in suboptimally controlled type 1 diabetes patients. The magnitude of the improvement in glycaemic control suggests an additive effect of the insulin pump, mealtime insulin dose advisor and CGM.

The use of sensor augmented pump therapy was also studied in **Chapter 9**. However, in this randomised controlled pilot trial, we investigated the efficacy of the therapy in patients with hyperglycaemia (>7.7 mmol/l) admitted to the coronary care unit (CCU) for acute myocardial infarction. Hyperglycaemia is a known risk factor for mortality after myocardial infarction, but previous trials were not able to lower the glucose in this patient group. Therefore we tested the sensor augmented pump therapy. 20 Patients were randomised to either sensor augmented pump therapy for 48 hours or standard care. Although effective in normalising glucose levels, sensor augmented pump therapy was associated with increased hypoglycaemia and workload for the nursing staff due to false positive alarms. Improvement of the device is awaited before continuing with large scale trials.

In **Chapter 10** a part of the development of sensor augmented pump therapy towards the artificial pancreas was studied. As two functions, insulin delivery and glucose sensing, are combined, one would like to physically integrate insulin delivery and glucose sensing as this would minimise the discomfort for the patient and increase the usability. Therefore we investigated the hypothesis that high local insulin concentrations would interfere with sensor readings in 10 type 1 diabetes patients using microdialyses CGM. We concluded that microdialysis CGM could be accurately performed at a mean distance of 0.9 cm from an insulin pump system in the normo- and hyperglycaemic ranges, and probably the hypoglycaemic range, during rapid rise and fall of blood glucose. This has important consequences for the development of a closed-loop system or artificial pancreas.
The development of the closed-loop system was further investigated in **Chapter 11**. To optimally integrate insulin delivery and glucose sensing, communication via an algorithm is essential. However, an effective algorithm has proven difficult to develop. In this pilot study we have investigated the effectiveness of an algorithm to treat postprandial glucose excursions in a closed-loop format. Indeed, the algorithm is as effective as standard care, and may even become superior, which we hope to demonstrate in a subsequent study.

In **Chapter 12** hyperglycaemia is approached from a different perspective. Of course, hyperglycaemia is not a constant phenomenon, but it will vary over time. This will be even more pronounced when treatment of hyperglycaemia is initiated. Earlier studies already suggested that this glucose variation may be harmful by itself. Because variation of glucose is always associated with the mean glucose, it is difficult to distinguish between these two. In this study, we investigated the association of glucose variability, using a newly developed measure of glycaemic variability, and mortality among 5728 patients admitted to the ICU. We found that high glucose variability was strongly associated with ICU and in-hospital death. High glucose variability combined with high mean glucose values was associated with highest ICU mortality. Low glucose variability seemed protective, even when mean glucose levels were elevated.

Every upside has its downside, as we show in **Chapter 13**. The downside of treating patients for hyperglycaemia in the ICU is that you will increase the risk of hypoglycaemia. Whether or not this is harmful is being debated and therefore we investigated the association between hypoglycaemia and mortality in the ICU. All first episodes of hypoglycaemia (glucose <= 2.5 mmol/l) were derived from 154015 glucose values in 5961 patients admitted to the ICU. Patients were considered to be exposed to hypoglycaemia from the event until the end of ICU admittance. Hypoglycaemia was indeed related to ICU mortality, also when adjusted for a daily adjudicated measure of disease severity, indicating a causal relationship.

Finally in **Chapter 14** we try to put the most important recent evidence of the NICE-SUGAR and Leuven studies in perspective, thereby including our data from an ICU population treated according to the most recent guidelines. Mean glucose during ICU admission turned out to be related to mortality by a U-shaped curve. A ‘safe range’ of glucose regulation in our population could be defined between 7.0
Summary and future considerations

and 9.0 mmol/l. The U-shaped curve may help to explain the increased mortality in
the intensively treated group of the NICE-SUGAR study but also the higher
mortality in the conventionally treated groups of the Leuven studies.

So, what should be done in the future? The application of sensor augmented pump
therapy for poorly regulated patients with diabetes mellitus type 1 has been proven
to be effective in lowering HbA1c, but not in preventing hypoglycaemia. However,
no trial so far has been designed for sensor augmented pump therapy with (severe)
hypoglycaemia as the primary outcome measure. Such a trial is expected and
warranted in the near future. The development of the closed-loop or artificial
pancreas is ongoing and future projects will hopefully bring this holy grail a little
bit closer by improving and designing algorithms for the communication between
glucose sensor and insulin pump. The use of sensor augmented pump therapy in a
(acute) clinical setting needs improvement, as shown in chapter 9. It could be a
most useful tool, as continuous glucose measurements, when accurate, should be
able to prevent hypoglycaemia, decrease nursing workload and capture glucose
variability. It should be realised that at a completely different patient group as
compared to patients with type 1 diabetes mellitus. Patients in an ICU or CCU
have other major problems next to their hyperglycaemia, which could influence the
accuracy of the glucose sensors. When writing this thesis, the TOPDOGS study is
being finalised. In this study factors influencing the effectiveness and accuracy of
glucose sensors in the ICU is being investigated in a large cohort and the results
are awaited eagerly. Finally, a pooled analysis of the NICE-SUGAR and Leuven
data is expected to provide treatment guidelines for treating hyperglycaemia,
glucose variability and avoiding hypoglycaemia in the ICU. For now, the avoidance
of hypoglycaemia by targeting for a safe-range seems advisable, considering the U-
shaped mortality curve.
Samenvatting en toekomstperspectief
Het onderwerp van dit proefschrift is hyperglykemie: een verhoging van het glucosegehalte in het bloed. De meest voorkomende oorzaak van hyperglykemie is de ziekte diabetes mellitus. Sinds de ontdekking van insuline is de levensverwachting van patiënten met diabetes mellitus enorm gestegen. Het blijft echter een aandoening waarbij patiënten rekening moeten houden met ernstige complicaties van de ziekte en een levenslange en hinderlijke behandeling.

Een minder bekende oorzaak van hyperglykemie is fysieke stress. Door bijvoorbeeld een operatie of een hartinfarct kan een dusdanige acute metabole ontregeling ontstaan dat het glucose stijgt. Waar men vroeger dacht dat deze tijdelijke hyperglykemie gunstig zou kunnen zijn voor het herstel, wordt het steeds duidelijker dat het eigenlijk zeer nadelig is voor de patiënt.

In DEEL I van dit proefschrift worden de gevolgen van hyperglykemie onderzocht, vooral in relatie tot het stollingssysteem en het optreden van trombose. Daarbij hebben we ons in het bijzonder gericht op de gevolgen van acute hyperglykemie, uitgelokt door een operatie. DEEL II van dit proefschrift gaat over het detecteren en behandelen van hyperglykemie. Tot op heden is het gebruikelijk dat de patiënt met diabetes een aantal maal per dag met een vingerprik in het bloed de hoogte van het glucose meet en daarop insuline spuit. Door de technische vooruitgang is het inmiddels mogelijk om met behulp van sensoren in de buikhuid continu het suikergehalte te meten en ook continu kleine hoeveelheden insuline middels een pomp af te geven. De effectiviteit van deze nieuwe behandelingstechniek hebben we onderzocht bij patiënten met diabetes mellitus en patiënten met hyperglykemie tijdens een hartinfarct. Tevens wordt geanalyseerd hoe deze nieuwe behandelingstechniek verder is te verbeteren. In de laatste hoofdstukken komt het detecteren van hyperglykemie op de Intensive Care (IC) aan bod en de nadelen van behandeling met insuline in deze situatie.

DEEL I

In Hoofdstuk 2 geeft een overzicht van de huidige literatuur met betrekking tot de rol van hyperglykemie in het stollingssysteem. Er is overtuigend bewijs dat zowel chronische als acute hyperglykemie het stollingssysteem activeren en de afbraak van een stolsel vertragen. Dit leidt tot een verhoogd risico op trombose. Het behandelen van hyperglykemie bij patiënten met diabetes mellitus blijkt het risico op trombotische aandoeningen, zoals een hersen- of hartinfarct, te verlagen. Echter, het effect van de behandeling van acute hyperglykemie is nog niet voldoende onderzocht in interventie trials.
Hoofdstuk 3 bevestigt het verband tussen hyperglykemie en stolling in een groep patiënten die werd onderzocht op de polikliniek op verdenking van een diep veneuze trombose in het been. Van deze personen hadden er 188 daadwerkelijk een trombose in het been. De controlegroep bestond uit 370 mensen die geen trombose bleken te hebben. Hoe hoger het glucose was bij presentatie op de polikliniek, hoe groter de kans was dat de patiënt inderdaad een trombosebeen had. Dit is de eerste keer dat de relatie tussen een trombosebeen en oplopend glucose is aangetoond en vervolgstudies zijn nodig ter bevestiging.


Hoofdstuk 5 bevestigt de suggestie die we hebben gedaan in hoofdstuk 4: verhoogde glucosewaarden na een heupoperatie voorspellen de latere ontwikkeling van veneuze trombose. Dit bleek uit een post-hoc analyse van 4 grote studies die waren uitgevoerd bij 12383 patiënten die electieve heup- of knieoperaties ondergingen. De belangrijkste uitkomstmaat was symptomatische veneuze trombose en “totale veneuze trombose” (gecombineerde uitkomstmaat van symptomatische en asymptomatische trombose met overlijden door welke oorzaak dan ook). Op dag één na de operatie bleken de gemiddelde glucosewaarden in de patiëntengroepen gestegen in vergelijking met preoperatieve waarden. Bij patiënten die een heupoperatie ondergingen was deze verhoging geassocieerd met een verhoogd risico op het ontwikkelen van symptomatische en “totale veneuze trombose”. Dit werd niet aangetoond bij patiënten die een knieoperatie ondergingen, wat mogelijk verklaard wordt door het verschil in de chirurgische procedure. Deze resultaten geven aan dat hyperglykemie kan ontstaan als gevolg van orthopedische chirurgie en bij heupoperaties ook bijdraagt aan de ontwikkeling van postoperatieve veneuze trombose.
Samenvatting en toekomstperspectief

In **Hoofdstuk 6** werd een andere patiëntengroep bestudeerd: bij 330 patiënten die een pancreatoduodenectomie ondergingen werd het glucose gemeten voor, tijdens en na de operatie. Ten gevolge van de operatie ontstond hyperglykemie en deze bleek een sterke voorspeller voor postoperatieve complicaties.

Uit al deze studies komt naar voren dat acute hyperglykemie kan worden veroorzaakt door pathofysiologische stress, zoals een operatie, ook zonder dat de patiënt diabetes mellitus heeft. Postoperatieve hyperglykemie blijkt geassocieerd met veneuze trombose na heupoperaties en met complicaties na een pancreatoduodenectomie. De logische volgende stap lijkt de preventie te zijn van perioperatieve hyperglykemie en het effect daarvan bestuderen in gerandomiseerde studies. Omdat de toepassing van intensieve insuline therapie peroperatief tijdrovend is en gepaard gaat met een verhoogd risico op hypoglykemie, kan ook gebruik van andere glucoseverlagende medicatie dan insuline worden overwogen. Te denken valt aan bepaalde orale medicatie en GLP-1 analoga.

**DEEL II**

**Hoofdstuk 7** wordt de huidige stand van zaken met betrekking tot de continue subcutane glucose sensoren, al dan niet in combinatie met de insulinepomp besproken. Uit meerdere studies blijkt inmiddels dat met behulp van continue glucose sensoren het HbA1c verlaagd kan worden bij volwassen, slecht gereguleerde maar gemotiveerde patiënten met type 1 diabetes, mits zij het apparaat verdragen. Het nut van het gebruik van sensoren ter preventie van hypoglykemie is nog niet bewezen. Hoewel een analyse van de kosteneffectiviteit nog moet worden uitgevoerd, is de verwachting dat sensoren in toenemende mate zullen worden vergoed door verzekeraars.

In **Hoofdstuk 8** worden de resultaten van de EURYTHMICS trial (EURopean (Y) trial To lower HbA1c by Means of an Insulin pump augmented by a Continuous glucose Sensor) gepresenteerd. De effectiviteit van behandeling van type 1 diabetes met een combinatie van glucose sensor en insulinepomp werd onderzocht in een gerandomiseerde studie in 8 Europese landen bij 83 patiënten met een HbA1c van 8.2% of hoger. De patiënten werden gerandomiseerd naar 26 weken behandeling met sensor gecombineerd met pomp voorzien van een maaltijd bolus-calculator of naar continueren van de behandeling met meerdaagse insuline injecties. We toonden aan dat therapie met sensor en pomp het HbA1c verlaagt met 1.21%. Deze
mate van HbA1c verlaging suggereert een gecombineerd effect van de glucose sensor, de insulinepomp en de bolus-calculator.

Ook in Hoofdstuk 9 werd pomp therapie in combinatie met glucose sensor onderzocht in een gerandomiseerde studie. Echter, nu werden 20 patiënten die werden opgenomen op de hartbewaking met een acuut hartinfarct en een verhoogd glucose (>7.7 mmol/l) gerandomiseerd naar behandeling met sensor gecombineerde pomptherapie of conventionele behandeling gedurende 48 uur. Eerdere onderzoeken slaagden er niet in om glucose effectief te verlagen in deze patiëntengroep, terwijl hyperglykemie een bekende risicofactor voor overlijden is. Met therapie met sensor en pomp bleek het inderdaad wel mogelijk om het glucose te verlagen, echter dit ging gepaard met een toename van hypoglykemie en werkdruk voor het verpleegkundig personeel. Voordat grotere gerandomiseerde studies worden opgezet, lijken verbeteringen aan de apparatuur gewenst.

Het verder integreren van de glucose sensor en de insulinepomp is onderzocht in Hoofdstuk 10. Dit moet uiteindelijk leiden tot de ontwikkeling van een kunstmatige pancreas. In dit hoofdstuk is onderzocht of het mogelijk is insuline afgifte en glucosemetingen op dezelfde plaats in het buikvet te verrichten. Dit zou de weg vrijmaken naar de ontwikkeling van één naald waarmee beide functies kunnen worden uitgevoerd, wat het ongemak voor de patiënt belangrijk zou verminderen. Bij 10 patiënten met type 1 diabetes onderzochten we de invloed van hoge concentraties insuline zo dicht mogelijk bij een continue microdialyse glucose sensor. Het bleek dat de sensor nauwkeurig blijft meten op een gemiddelde afstand van 0.9 cm vanaf de injectieplaats van de insulinepomp. Zowel bij hoge als normale glucosewaarden bleven de metingen nauwkeurig en dit leek ook het geval in het hypoglykemische gebied. Ook tijdens het snel stijgen en dalen van glucose waren de metingen van de sensor niet minder nauwkeurig. Deze resultaten hebben belangrijke consequenties voor het verder ontwikkelen van de kunstmatige pancreas.

Ook Hoofdstuk 11 heeft betrekking op de ontwikkeling van een kunstmatige pancreas. Om insuline afgifte te laten plaatsvinden op basis van gemeten continue sensor waarden is communicatie tussen deze twee functies via een algoritme essentieel. De ontwikkeling van een dergelijk algoritme is een uitdaging gebleken. In dit onderzoek is de effectiviteit van een algoritme om postprandiale glucose excursies te behandelen onderzocht in een gesloten systeem, dus zonder interventie
van de arts of patiënt. Het algoritme bleek even effectief als de standaard behandeling, wellicht zelfs iets beter, en een vervolgstudie is inmiddels gaande.

In **Hoofdstuk 12** bekijken we hyperglykemie vanuit een andere invalshoek. Hyperglykemie is geen constant fenomeen, maar de glucosewaarden zullen variëren over de tijd. Ook behandeling van hyperglykemie heeft invloed op de variabiliteit van glucose. Uit eerder onderzoek is gebleken dat deze glucose variatie op zichzelf ook schadelijk kan zijn. Omdat de mate van variatie samenhangt met het gemiddelde bloedglucose is het lastig om de gevolgen van beide fenomenen apart te onderzoeken. In dit hoofdstuk hebben we daarom een nieuwe maat voor glucose variabiliteit ontwikkeld. Bij 5728 patiënten is onderzocht wat de associatie is tussen glucose variabiliteit en mortaliteit op de IC. Een verhoogde glucose variabiliteit bleek duidelijk geassocieerd met een toename van het aantal patiënten dat overleed. De combinatie van een hoog gemiddeld glucose tijdens opname en hoge variabiliteit bracht het hoogste sterftecijfer met zich mee. Een lage glucose variabiliteit leek echter te beschermen tegen overlijden.

Elke behandeling is geassocieerd met bijwerkingen, zoals is te lezen in **Hoofdstuk 13**. De standaard behandeling van hyperglykemie op de IC is insuline therapie, waarmee het risico op hypoglykemie toeneemt. In de huidige literatuur bestaat verschil van mening over de vraag of deze hypoglykemie schadelijk is. Daarom onderzochten wij de relatie tussen hypoglykemie en mortaliteit op de IC. Alle eerste episodes van een glucose \(\leq 2.5 \text{ mmol/l} \) werden onderzocht in een groep van 5961 IC patiënten. Patiënten werden beschouwd als zijnde beroepsgesteld aan hypoglykemie vanaf het moment van de episode tot aan het einde van de IC opname. Er bleek inderdaad een duidelijke relatie te bestaan tussen hypoglykemie en sterfte op de IC, ook na correctie voor ernst van ziekte van de patiënt. Dit suggereert een causaal verband.

Tot slot hebben we in **Hoofdstuk 14** geprobeerd de twee belangrijkste IC trials (NICE-SUGAR en Leuven) naar de effectiviteit van insuline therapie op de IC in perspectief te plaatsen met behulp van de data uit een IC populatie. Het gemiddelde glucose tijdens IC opnames blijkt zich te verhouden tot sterfte op de IC via een U-curve. De laagste sterfte, ofwel het veilige gebied, bevindt zich in de bestudeerde populatie tussen de 7.0 en de 9.0 mmol/l. Deze U-curve kan wellicht de interpretatie van zowel het hoge sterftecijfer in de intensief behandelde groep van
de NICE-SUGAR studie, alsook de hogere sterfte in de conventioneel behandelde groepen van de Leuven studies vergemakkelijken.

Wat kunnen we nu in de nabije toekomst verwachten aan verdere ontwikkelingen en studies? De toepassing van pomptherapie gecombineerde met sensor bij slecht gereguleerd patiënten met type 1 diabetes is bewezen effectief ter verlaging van het HbA₁₀, maar niet bij het voorkomen van hypoglykemie. Er zijn echter nog geen gerandomiseerde studies gepubliceerd waarin het voorkomen van hypoglykemie bij het gebruik van glucose sensoren specifiek is onderzocht. Het is belangrijk dat een dergelijke studie gaat worden uitgevoerd.

De ontwikkeling van de kunstmatige pancreas is nu volop gaande en vooral de verbeterde algoritmes om de glucose sensor en insulinepomp met elkaar te laten communiceren zijn veelbelovend. Bij het gebruik van de glucose sensor gecombineerd met insulinepomp in de acute klinische setting is, zoals wij hebben laten zien, nog veel ruimte voor verbetering. Het is in potentie een nuttig apparaat aangezien de continue glucose metingen, indien voldoende nauwkeurig geregistreerd, hypoglykemie en glucose variabiliteit kunnen helpen voorkomen met daarbij een vermindering van de werkdruk van het verpleegkundig personeel. Men moet zich echter wel realiseren dat het hier gaat om een totaal andere patiëntengroep dan de patiëntengroep met type 1 diabetes. Patiënten op de hartbewaking en de IC hebben naast hun hyperglykemie andere pathologie, die direct de werking van de glucosesensoren kan beïnvloeden. Terwijl dit proefschrift wordt geschreven, wordt ook de laatste hand gelegd aan een studie waarin een aantal bijkomende factoren op de IC worden onderzocht, die de nauwkeurigheid en effectiviteit van glucose sensoren zouden kunnen beïnvloeden, zoals verminderde weefselpersfusie en temperatuurschommelingen (de TOPDOGS studie). Tenslotte wordt een gezamenlijke analyse verwacht van de NICE-SUGAR en Leuven data, Deze analyse kan vermoedelijk leiden tot het vaststellen van definitieve richtlijnen voor de behandeling van hyperglykemie en de preventie van hypoglykemie en glucose variabiliteit. Op dit moment lijkt het, gezien de U-vormige sterfte curve, verstandig om hypoglykemie in ieder geval te vermijden en dus een veilige glucose range aan te houden bij patiënten op de IC.
List of Publications
List of Publications


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