What goes up must come down: glucose variability and glucose control in diabetes and critical illness
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Chapter 11

Special considerations for the diabetic patient in the intensive care unit: targets for treatment and risks of hypoglycaemia

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Abstract

Due to the diabetes pandemic the number of diabetic patients admitted to the ICU increases. Diabetic patients admitted to the ICU are more vulnerable for developing complications as compared to non-diabetic patients, but this does not directly translate into higher mortality rates. However, mortality might differ per admission diagnosis. Hyperglycaemia is common in diabetic as well as non-diabetic critically ill patients, but probably chronic hyperglycaemia is pathophysiologically different from acute hyperglycaemia. As opposed to non-diabetic patients, there is discussion about the association between hyperglycaemia and mortality in diabetic patients. They do not seem to benefit from strict glycaemic control and also glucose variability appears less harmful, although clinical trials in diabetic populations have not been performed yet. Diabetes is a risk factor for hypoglycaemia and evidence suggests that even near-normal glucose levels are associated with worse outcome. Taking this together, it is suggested to strive for moderate targets when treating hyperglycaemia in critically ill diabetic patients.
I. Introduction

Hyperglycaemia is common in all critically ill patients, not only in those with a prior diagnosis of diabetes mellitus. Hyperglycaemia in the critically ill is associated with increased mortality but large intervention studies evaluating the treatment of intensive care unit (ICU) hyperglycaemia by intensive insulin therapy, show conflicting results. There is no definite answer to the question whether and how tight hyperglycaemia of critically ill patients has to be treated. Also, there may be a difference in outcome between subgroups of patients. More and more the idea evolves that chronic hyperglycaemia in critically ill patients with diabetes is pathophysiologically different from acute hyperglycaemia in those without previously diagnosed diabetes, with consequences in the hyperglycaemic as well as in the hypoglycaemic range. This could mean that treatment targets and strategies in patients with diabetes should differ from those without diabetes.

If this hypothesis is true, the next question is whether undiagnosed diabetes should be treated as patients with known diabetes or as patients without diabetes and a big challenge for ICU physicians would be to unmask all patients with diabetes admitted at the ICU. A large proportion of the patients admitted are unconscious hampering adequate history taking and the medical history may be incomplete. Plasma glucose values will not distinguish between those with and without diabetes due to the fact that hyperglycaemia is also very common in non-diabetic critically ill patients. Therefore some plead to measure HbA1c in all admitted patients to diagnose pre-existing diabetes, but this discussion lies outside the scope of this review.

In this review we will give an overview of the current literature on morbidity and mortality in diabetic ICU patients with special consideration to glucose regulation, insulin treatment and hypoglycaemia. For this purpose we searched MEDLINE for studies conducted at any ICU concerning patients with diabetes, solely or in comparison with patients without diabetes, without any restriction with respect to publication date. Randomised controlled trials as well as observational studies were included. We distinguished between studies regarding glucose regulation and studies looking at morbidity and mortality of patients with diabetes at the ICU independent from glucose regulation. Where possible the results are presented separately for different subpopulations of ICU patients, for example cardiac surgery patients.

II. The diabetic patient in the ICU

A. Are diabetic patients at higher risk for morbidity?
As a result of the diabetes pandemic in the western world, the number of diabetic patients...
admitted at the ICU also increases. Are there any consequences of this increase? It is known that patients with diabetes are vulnerable for the development of complications during ICU admission: immune cell functions are hampered which theoretically promotes the incidence of various kinds of infections and there is a prothrombotic shift in coagulation and fibrinolysis. Also the presence of diabetic complications as micro- and macrovascular damage might have an effect on morbidity and perhaps mortality as compared to non-diabetic individuals.

Nearly all studies looking at the incidence of complications in diabetic patients admitted at the ICU support the hypothesis that they have increased morbidity. In cardiac surgery patients all studies confirm that diabetes is a risk factor for postoperative complications such as infections and, perhaps as a consequence, longer ICU and hospital stay. The same goes for diabetic trauma patients. Also in mixed ICU populations diabetes seems to be a risk factor for the development of (severe) infections and acute organ failure. Interestingly, diabetic patients seem to have a decreased risk of developing acute respiratory distress syndrome (ARDS). This could be explained by the abovementioned impairment in immune function promoting infections, as the overzealous activation and recruitment of circulating neutrophils into the lung is involved in the pathogenesis of ARDS. However, although the evidence points to an increased complication risk in diabetic patients admitted at the ICU, there are also studies which could not confirm this for development of nosocomial pneumonia and bacteriuria and as far as the authors are aware no meta-analysis has been performed so far.

B. Are diabetic patients at higher risk for mortality?

With a probably higher complication risk and increased length of stay, one would also expect an increased mortality risk for diabetic ICU patients. Studies in cardiac surgery patients indeed show increased mortality rates for all diabetic patients or in those with long-term complications. On the other hand, medical diabetic patients or patients admitted in mixed ICU’s having an infection do not seem to have increased mortality. Data from mixed ICU populations without further specification are less conclusive. showed even a lower adjusted mortality risk for diabetic patients which was confirmed by the publication of the largest cohorts reported so far, 1,509,890 and 36,414 diabetic patients. But also increased and similar mortality rates have been described.

It is intriguing to conclude that some diabetic ICU patients are perhaps protected and others have a higher mortality risk. It might be that for example diabetic patients undergoing cardiac surgery have a larger number of affected coronary vessels contributing to the higher mortality in that group. The relative tolerance for hyperglycaemia, which will be discussed in the next section, might contribute to decreased mortality rates,
but all proposed explanations are still only speculative. To further clarify the relation between diabetic status and mortality, a meta-analysis making distinction between subgroups of patients is needed.

III. Glucose regulation

A. Is hyperglycaemia deleterious to diabetic ICU patients?
In patients without diabetes marked critical illness associated hyperglycaemia is undisputedly related to morbidity and mortality\textsuperscript{1,33}. Critical illness-induced hyperglycaemia is caused by inflammatory and neuro-endocrine derangements in these patients leading to high hepatic glucose output and insulin resistance\textsuperscript{34}. In patients with diabetes hyperglycaemia is already a pre-existing situation, although critical illness may of course further derange blood glucose values by the above mentioned mechanisms.

Several studies examined the relation between hyperglycaemia and outcome in critically ill patients with diabetes. In diabetic cardiac surgery patients hyperglycaemia above 11.1 mmol/l seems independently associated with increased wound infection rates\textsuperscript{22,35} as well as mortality and length of hospital stay\textsuperscript{35} (to convert from mmol/l to mg/dl divide by 0.0555). Contrary, Reyes et al.\textsuperscript{36} did not find an association between hyperglycaemia and complication rates in this group of patients, but in their study glucose levels were very well regulated (mean [SD] postoperative BG 7.6 [2.5] mmol/l).

In mixed ICU populations the relationship between hyperglycaemia and mortality in diabetic patients is less clear. Three studies containing large cohorts of diabetic patients do report a relation between hyperglycaemia and mortality. Rady et al.\textsuperscript{37} retrospectively analyzed 1,083 ICU patients with diabetes and found that patients with median glucose levels above 11.1 mmol/l showed increased mortality compared with patients with median glucose levels between 4.4 and 11.1 mmol/l. In the latter group median glucose was not related to mortality rates. Graham et al.\textsuperscript{29} performed a retrospective analysis of 36,414 diabetic patients from the Mayo Clinic (Rochester, MN, USA). They found increased hospital mortality rates in patients with peak glucose levels above 9.1 mmol/l compared with patients with peak glucose levels between 7.2 and 9.1 mmol/l. Interestingly, patients with peak glucose levels lower than 7.2 mmol/l were also found to have higher mortality rates. However, no analyses were performed adjusting for possible confounders. Falciglia et al.\textsuperscript{38} did adjust for an important confounder: severity of disease. In a retrospective cohort of 78,142 diabetes patients subdivided into groups with increasing mean glucose levels, increasing hyperglycaemia was significantly associated with higher hospital mortality compared to normoglycaemia (3.9-6.1 mmol/l).
In contrast with these findings, Egi et al. 28 could not confirm the deleterious effect of hyperglycaemia in diabetic patients. In a cohort of 728 patients with diabetes, no significant difference in ICU- and hospital mortality was found when analyzing four equally sized groups of patients with increasing mean glucose levels, the glucose of the lowest group ranging from 8.1 mmol/l to below. Also mean glucose values were comparable between diabetic survivors and non-survivors (mean [SD] glucose 9.5 [2.9] and 9.6 [2.8] mmol/l, respectively) 39. Two other studies including 574 (21.2%) 40 and 188 (22.7%) 26 diabetic patients investigated the effect of admission glucose on mortality but no effect of hyperglycaemia higher than 11.1 mmol/l was seen. It might be possible that the degree of pre-existing hyperglycaemia, expressed as HbA1c, alters the association between acute glycaemia and mortality. A recent study including 415 patients with diabetes shows that in patients with preadmission HbA1c levels above 7.0%, the higher the glucose levels during admission, the lower the hospital mortality, in contrast to patients with HbA1c levels under 7.0%, where higher glucose levels during admission translate into higher mortality rates 41.

Without exception it has been found that at any given mean glucose level in the hyperglycaemic range the mortality of patients with diabetes is lower than the mortality of non-diabetic patients. The cut-off values where this effect occurs vary however. Rady showed already an increased mortality rate and Falciglia an increased adjusted odds-ratio for mortality in non-diabetic patients compared to diabetic patients in the subgroup with a median 37 or mean 38 glucose between 6.2 and 8.0 mmol/l. This was not confirmed in other studies which report a significant difference in mortality in favour of patients with diabetes only for a mean glucose level of 8.0 mmol/l and above 39 or a peak glucose level of 9.1 mmol/l and above 29. Another study investigating only admission glucose values above 11.1 mmol/l shows also lower mortality rates for patients with diabetes 26.

The different effects of hyperglycaemia in ICU patients with and without diabetes suggest that acute hyperglycaemia in critical illness and chronic hyperglycaemia in diabetes are two distinct pathophysiological entities. Adaptation to hyperglycaemia might be a key mechanism. Acute hyperglycaemia and inflammation induce e.g. oxidative stress which causes endothelial damage 42. It is possible that patients with diabetes are already adapted to these insults and therefore better tolerate episodes of hyperglycaemia compared with non-diabetic patients, whose cellular adaptation mechanisms are not yet activated. Attractive as it may be, this hypothesis is not substantiated any further in the literature.

B. Do diabetic patients benefit from intensive insulin therapy?
Apart from whether there is any association between hyperglycaemia and mortality in diabetic ICU patients, the relevant clinical question is whether they would benefit from glucose lowering therapy. Several large clinical studies addressed this question but none
of them was specifically designed to look at the effect of intensive insulin therapy (IIT) in diabetes patients. The results presented here are therefore derived from sub-analyses except for three trials investigating intensive insulin therapy in diabetes patients during cardiac surgery. Characteristics of the trials are presented in Table 1.

In 2001 van den Berghe et al. awoke the intensive care community publishing the results of the so-called first Leuven study. They reported that IIT, with an achieved mean [SD] morning blood glucose of 5.7 [1.1] mmol/l, in the surgical ICU significantly reduced ICU and hospital mortality compared with conventional treatment (mean [SD] 8.5 [1.8] mmol/l), with an absolute mortality reduction from 8.0 to 4.6%. This was mainly attributed to patients with an ICU stay of more than 5 days (mortality reduction from 20.2 to 10.6%). 204 of the 1548 patients included in this study had a history of diabetes. Subanalysis of this group showed somewhat less survival benefit of IIT in diabetic patients with an ICU stay longer than 5 days (16.0 to 9.5%), although it remained a significant effect. In the second Leuven study, performed in a medical ICU, the reduction in mortality with IIT was restricted to patients with an ICU stay of more than 3 days (52.5 to 43.0%, \( P = 0.009 \)). For the subgroup of patients with diabetes (n = 203) IIT showed no survival benefit overall and also not in those admitted to the ICU for more than 3 days.

Other randomised controlled trials (RCT’s) investigating the effect of intensive insulin therapy on mortality with sub-analyses for patients with diabetes were performed at mixed surgical and medical ICU’s, without making distinction between surgical and medical patients. In all these studies IIT did not show survival benefit over conventional glucose control in patients with diabetes. Also when analyzing pooled data from both Leuven trials no benefit of IIT was seen in the diabetic patients. The achieved glucose levels in the IIT group of the pooled analysis ranged from 5.8 to 6.5 mmol/l and in the conventional group from 8.0 to 9.5 mmol/l. The NICE-SUGAR trial published in 2009 included the largest population of diabetes patients (n = 1211) and achieved mean (SD) glucose values of 6.4 (1.0) and 8.0 (1.3) mmol/l in the total population. In this subgroup the benefit tended towards the conventional treatment, just like the overall outcome. Pooling these data for the purpose of this manuscript, using Review manager version 5 (The Cochrane Collaboration, Oxford, UK), shows no benefit of intensive or conventional treatment regarding mortality with little heterogeneity \( (I^2 = 17\%); \) Figure 1). The negative results in the mixed populations are supported by analyses comparing mortality rates before and after the implementation of an IIT protocol showing no significant decrease in mortality with IIT in patients with diabetes.

The use of IIT in cardiac surgery patients however shows more positive results. Lazar et al. showed in 141 diabetic patients who underwent cardiac surgery that those receiving IIT during surgery had a survival advantage over the initial two years after surgery and
Table 1 Main characteristics of intervention studies on intensive insulin therapy in diabetic ICU patients

<table>
<thead>
<tr>
<th>Study</th>
<th>Type</th>
<th>Population</th>
<th>n DM</th>
<th>Intensive achieved BG</th>
<th>95% CI/SD</th>
<th>Conventional achieved BG</th>
<th>95% CI/SD</th>
<th>Mortality (%)</th>
<th>IIT</th>
<th>C</th>
<th>type</th>
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<tr>
<td>van den Berghe 2001 3</td>
<td>RCT</td>
<td>Surgical</td>
<td>204</td>
<td>5.7</td>
<td>1.1</td>
<td>8.5</td>
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<td>4.0</td>
<td>5.8</td>
<td>ICU</td>
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<tr>
<td></td>
<td>RCT</td>
<td>Surgical &gt;5d ICU</td>
<td>46</td>
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<td>na</td>
<td>na</td>
<td>9.5*</td>
<td>16.0</td>
<td>ICU</td>
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<td></td>
</tr>
<tr>
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<td>RCT</td>
<td>Medical</td>
<td>203</td>
<td>5.7</td>
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<td>8.5</td>
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<tr>
<td></td>
<td>RCT</td>
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<td>117</td>
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<tr>
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<td>407</td>
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<td>1.3</td>
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<td>1.3</td>
<td>8.4</td>
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<td>23.2</td>
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<tr>
<td>Brunkhorst 2008 44</td>
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<td>163</td>
<td>6.2</td>
<td>6.1-6.3</td>
<td>8.4</td>
<td>8.2-8.6</td>
<td>25.0</td>
<td>31.9</td>
<td>28-day</td>
<td>ICU</td>
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<tr>
<td>Arabi 2008 41</td>
<td>RCT</td>
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<td>208</td>
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<td>1.9</td>
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<td>De La Rosa 2008 45</td>
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<td>6.5</td>
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<td>8.2</td>
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<td>ICU</td>
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<tr>
<td>Finfer 2009 2</td>
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<td>1,211</td>
<td>6.4</td>
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<tr>
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<td>Mixed</td>
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<td>10.4</td>
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<td>22.6</td>
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<td>Mixed</td>
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<td>7.1</td>
<td>6.2-8.3</td>
<td>10.2</td>
<td>8.1-12.6</td>
<td>26.5</td>
<td>29.4</td>
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<td>Cardiac surgery</td>
<td>141</td>
<td>7.5</td>
<td>0.2</td>
<td>14.8</td>
<td>0.3</td>
<td>1.4*</td>
<td>10.0</td>
<td>2-year</td>
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<tr>
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<td>Pre-post</td>
<td>Cardiac surgery</td>
<td>3,554</td>
<td>9.8</td>
<td>1.7</td>
<td>11.9</td>
<td>2.3</td>
<td>2.5*</td>
<td>5.3</td>
<td>Hospital</td>
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</table>

Summary of the main characteristics of the intervention studies investigating the effect of intensive insulin therapy (IIT) in critically ill patients with diabetes. Glucose values achieved are of the total population and depicted in mmol/l with 95% confidence interval or standard deviation. Outcome is given as mortality percentages. *P = <0.05 favouring IIT. See for meta-analysis Figure 1. BG, blood glucose; C, conventional treatment; DM, diabetes mellitus; ICU, intensive care unit; pre-post, era of conventional treatment (pre) compared with an era of intensive treatment (post); RCT, randomised controlled trial.
also shorter postoperative length of stay, decreased episodes of recurrent ischemia and less wound infections. This RCT was supported by a pre-post analysis showing that IIT was protective for hospital mortality and decreased length of stay but interestingly not post-operative infection rates after cardiac surgery. It has to be noted however that the achieved blood glucose levels in the studies including cardiac surgery patients lie above those conducted in the ICU. The achieved mean glucose in the intervention group ranged between 7.5 and 9.8 mmol/l, which is roughly comparable with the mean glucose of the conventionally treated ICU groups, and in the conventionally treated group between 11.9 and 14.8 mmol/l, which are glucose levels associated with increased mortality and morbidity in the observational studies. Therefore it is unknown whether more intensive glycaemic control aiming at glucose levels below 7.0 mmol/l is beneficial compared to moderate glycaemic control in cardiac surgery patients. A study performed by Gandhi et al. in 2006 was designed to assess this question and they achieved glucose levels after surgery of 6.3 (SD 1.6) mmol/l in the IIT group and 8.7 (2.3) mmol/l in the conventionally treated group. Unfortunately, the number of diabetic patients was too small (n = 37) and the overall mortality rate too low (1%) to perform subgroup analyses, though all 4 deaths occurred in the IIT group.

In summary, these data show that survival in mixed surgical/medical diabetic ICU patients treated with strict glycaemic control (mean glucose 5.8-6.5 mmol/l) is not different from patients treated with moderate glycaemic control (mean glucose 8.0-9.5 mmol/l). In diabetic cardiac surgery patients, moderate glycaemic control (mean glucose 7.5-9.8 mmol/l) has shown better results than loose glycaemic control (mean glucose 11.5-14.8 mmol/l). This implies that moderate glycaemic control aiming at glucose levels between 7.5 and 10.0 mmol/l is perhaps the best treatment for all critically ill diabetic patients, also because the lower the target, the more hypoglycaemic events occur.
IV. Hypoglycaemia

An important side-effect of insulin treatment is the occurrence of hypoglycaemia. All intervention studies of intensive insulin therapy report a substantial increase in hypoglycaemia incidence with intensive insulin therapy compared to less intensive therapy. Besides the use of insulin, also the presence of diabetes is a risk factor for the occurrence of severe hypoglycaemia, defined by cut-off levels of 3.3 mmol/l, 2.5 mmol/l as well as 2.2 mmol/l, independent of insulin dose at the time of the event. Patients with a prior diagnosis of diabetes may have an impaired counterregulatory response hampering adequate reaction to overdosed exogenous insulin, likely explaining these findings.

In mixed populations, without distinction between patients with or without diabetes, the occurrence of severe hypoglycaemia seems to be associated with mortality independently from severity of disease. Moreover, there is evidence that not only severe hypoglycaemia using the diabetes outpatient definition of 2.2 mmol/l but also glucose levels already lower than 4.7 mmol/l are harmful in critically ill patients. Unfortunately, such association studies have not been performed separately in diabetic patients. One study comparing nadir glucose values between diabetic survivors and non-survivors demonstrated significantly lower values in non-survivors (4.9 [2.6] and 5.7 [2.7] mmol/l, P = 0.02).

When comparing mortality rates of patients with and without diabetes in the lower glycaemic range a notable phenomenon is seen. Mortality rates at any given hyperglycaemic glucose level are higher in non-diabetic patients compared with diabetic patients as shown previously, but in the lower glucose range the opposite seems to occur. Graham showed hospital mortality rates to be significantly higher in diabetic ICU patients with peak glucose values below 7.2 mmol/l compared with non-diabetic patients in the same glucose range (P = 0.004). Krinsley reported similar findings for diabetic versus non-diabetic patients with mean glucose values under 6.6 mmol/l. Both studies show unadjusted results only. The finding that diabetic patients show higher absolute mortality rates when having a lower mean glucose during admission was confirmed by Egi et al. for mean glucose values between 4.4 and 6.1 mmol/l. But when adjusting also for severity of disease, the significant effect of diabetes on ICU and hospital mortality in this glucose range disappeared, although a trend remained visible; OR (95% CI) 0.33 (0.10-1.16, P = 0.08) and 0.45 (0.18-1.14, P = 0.09) for non-diabetic patients versus diabetic patients regarding ICU and hospital mortality, respectively. In the latter study no absolute mortality difference between the two groups was seen looking at mean glucose values lower than 4.4 mmol/l.
These findings show that diabetic patients are not only at risk for severe hypoglycaemia but also suggest a relative intolerance for normal and hypoglycaemic glucose values compared with patients without diabetes, although firm evidence is lacking.

V. Glucose variability

Glycaemic variability is a consequence of severe illness and associated with intensive insulin therapy. Also in diabetic outpatients, shortage of endogenous insulin production, presence of insulin resistance and/or diminished counter-regulatory responses cause instability of plasma glucose levels. Whether there is a negative effect of glucose variability over and above pure hyperglycaemia seems dependent on the patient population. In various adult and pediatric critically ill populations glucose variability is strongly associated with mortality independent of the overall glycaemic status \(^{48,57-60}\), but the effect of short-term glucose fluctuations in patients with diabetes outside the hospital remains subject of debate \(^{61}\). However, no intervention study specifically aiming at lowering glucose variability in diabetic patients at the ICU has been performed yet, although emerging data in diabetes outpatients suggest that lowering glucose variability does not result in improved outcome \(^{62}\). It is therefore interesting to investigate whether glucose variability is deleterious in diabetic critically ill patients.

Diabetic postoperative cardiac surgery patients \(^{63}\) as well as diabetic patients in mixed ICU populations \(^{48,54}\) show larger glycaemic variability than non-diabetic patients. Only two studies looked at the effect of glucose variability in critically ill diabetic patients. Egi et al. did not find increasing mortality in quartiles of increasing glucose variability (assessed as standard deviation) and ICU or hospital survival in 728 diabetic patients in a mixed ICU \(^{28}\), except for an univariate comparison of mortality rates between the lowest and highest glucose variability quartile, that is a standard deviation lower than 1.7 mmol/l versus 2.5-3.5 mmol/l, respectively \((P = 0.002)\). In the non-diabetic population in this study the standard deviation was an independent and strong predictor for mortality. Krinsley showed no association between glucose variability (assessed as coefficient of variation) and mortality in multivariate analysis of 942 diabetic predominantly medical ICU patients \(^{48}\), which is in contrast with their earlier findings in a population with only 23.8% patients with diabetes \(^{58}\). There was however a marked increase in mortality across increasing coefficient of variation strata in the subgroup of patients with the lowest mean glucose values (3.9-5.5 mmol/l). This is possibly due to the occurrence of hypoglycaemia, increasing both glucose variability and mortality, but no analysis was presented adjusting for hypoglycaemia.

In conclusion, it is evident that patients with diabetes have higher glucose variability during ICU stay but high glucose variability seems to be less harmful than in non-diabetic
patients. These results are in line with the observation that hyperglycaemia is more detrimental in non-diabetic patients. It has to be noted though that no intervention studies looking at the effect of specifically lowering glucose variability have been performed in critically ill diabetic as well as in non-diabetic patients.

VI. The role of continuous glucose monitoring in the ICU

At this time glucose control is practiced by means of frequent point-of-care measurements. Given the critical role of hypoglycaemia and glucose variability, the lack of information in between those measurements may be of importance. Continuous glucose monitoring (CGM) could be a useful tool in ICU glucose regulation by decreasing severe hypoglycaemia frequency and possibly increasing time in target range. However, accuracy results of subcutaneous CGM systems are inconsistent and seem dependent on the population and type of sensor used, but recent results in cardiac surgery and medical ICU patients are promising. In addition to subcutaneous glucose monitoring, also intra-vascular glucose monitoring devices are being developed with good results regarding accuracy. Future studies should investigate the benefit of these systems.

VII. Summary

As a consequence of the increasing incidence of diabetes throughout the world, the number of diabetic patients admitted at the ICU is growing. This needs attention since their treatment is in some aspects different from patients without diabetes. Nearly all studies show that diabetic patients suffer from more complications and have longer ICU and hospital length of stay. Mortality rates however are not simply higher. Diabetic cardiac surgery patients do have a decreased survival as compared to non-diabetic patients but data from medical ICU populations do not show a difference in mortality between diabetic and non-diabetic patients. In mixed populations there is even evidence that diabetic patients are relatively protected, however the data is not conclusive as there are also studies showing equal or increased mortality rates. A meta-analysis on this topic is needed. Hyperglycaemia is common in diabetic critically ill patients. There is discussion about the association between hyperglycaemia and mortality in this patient group but severe hyperglycaemia, above 11.1 mmol/l, is considered harmful and it seems useful to lower these high values with insulin therapy. Considering the currently available data on implementing insulin therapy, moderate glycaemic control is equally effective in reducing mortality compared with strict glycaemic control, the latter increasing hypoglycaemia substantially. This is of concern since diabetic patients are more prone to develop severe hypoglycaemia which is associated with mortality and it is suggested
that they are already intolerant for glucose values considered normoglycaemic, although conclusive evidence is lacking. Therefore we recommend to treat critically ill diabetic patients with moderately intensive insulin therapy aiming at blood glucose levels between 7.5 and 10.0 mmol/l, in that way avoiding extreme hyperglycaemia as well as normo- and hypoglycaemia. Currently there are insufficient arguments to specifically lower glucose variability, but intervention trials on this topic are awaited.

Our conclusions regarding the glucose target for ICU admitted diabetic patients support the recommendations of the American Association of Clinical Endocrinologists and the American Diabetes Association \(^7\), that for critically ill patients in general insulin treatment should be initiated at a threshold of 10.0 mmol/l and a glucose range of 7.8 to 10.0 mmol/l should be maintained. This consensus statement does not distinguish between patients with or without previously diagnosed diabetes. We think that it is important to add the presence of diabetes to the clinical situations that increase the risk for hypo- and hyperglycaemia.

**Practice Points**

- Diabetic patients are at high risk for developing complications in the ICU
- Glucose control needs attention also in diabetic patients
- We recommend to maintain glucose levels between 7.5 and 10.0 mmol/l in diabetic patients
- Hypoglycaemia and extreme hyperglycaemia should be vigorously avoided since these are associated with mortality
- Currently there are insufficient arguments to specifically lower glucose variability

**Research Agenda**

- A meta-analysis has to be performed to objectify the influence of diabetes on mortality risk in (subgroups of) critically ill patients
- Larger trials are needed to assess the effect of intensive insulin therapy in different critically ill diabetic populations
- The threshold level below which glucose values are harmful in critically ill diabetic patients needs to be determined
- Trials are needed to assess the effect of specifically lowering glucose variability
References

inflammatory responses in patients with severe sepsis. Crit Care Med 38: 539-545