What goes up must come down: glucose variability and glucose control in diabetes and critical illness
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Summary and future considerations

This thesis is about the effects and treatment of glucose peaks in chronic and acute hyperglycaemia. It addresses the question whether it is beneficial to curb these glucose peaks: must all what goes up come down? In Part I, the consequences of glucose variability in diabetes were studied with respect to oxidative stress, which is associated with endothelial damage, and two chronic complications of diabetes, neuropathy and cardiovascular events. Part II of this thesis discusses hyperglycaemia in critical illness. First, an optimal glucose target range for critically ill patients was proposed and a new method to reach this target range, subcutaneous continuous glucose monitoring (CGM), was tested for accuracy and reliability. Second, the implications of the presence of diabetes in a critical care setting were investigated with respect to glucose regulation and mortality.

Part I

In Chapter 2 we give an overview of the available methods to measure glucose variability and review the evidence for its importance in addition to mean glucose. A large variation in the number and duration of glucose peaks exists between patients with similar haemoglobin A1c levels, but to date there is no “gold standard” for quantifying glucose variability. The standard deviation from the mean seems the most extensively used and mathematically best validated measure. In in vitro, animal and experimental human studies, glucose peaks increase oxidative stress. However, the evidence for an independent effect of glucose variability on oxidative stress and long-term diabetic complications in type 1 and type 2 diabetes patients is marginal, and possibly limited to poorly regulated type 2 diabetes patients on oral glucose lowering drugs. Contrary, in the critically ill glucose variability is indisputably associated with mortality.

To understand the different findings of the effect of glucose variability in different diabetic populations, we investigated in Chapter 3 at which glucose level the glucose-dependent effects on vascular homeostasis first occur, and whether this is an on-off phenomenon with a threshold or a continuous relationship. A stepwise glucose clamp was performed in healthy humans, stabilizing plasma glucose levels for two hours at 6.0, 8.0, and 10.0 mmol/l successively. The effect of increasing glucose on oxidative stress, coagulation and fibrinolysis, and the endothelial glycocalyx were investigated. The results of this study reveal that changes to vascular homeostasis start already at near normal glucose levels. The increase in oxidative stress was dose-dependent and coagulation activation showed a threshold already at 6.0 mmol/l. Absence of a threshold or a threshold at such a low level do not support a role for glucose variability in oxidative stress and coagulation activation.
This conclusion was supported by the results described in Chapters 4 and 5. In Chapter 4, the relation between glucose variability, measured by continuous glucose monitoring, and oxidative stress, measured by 24-hr excretion of 8-iso prostaglandin F$_{2\alpha}$, was assessed in 24 well-regulated type 2 diabetes patients on oral glucose lowering drugs. No relevant relationship was found between glucose variability and oxidative stress. In Chapter 5 a mealtime insulin approach was compared with a basal insulin regimen in a cross-over study including 40 type 2 diabetes patients regarding glucose regulation and the effects on oxidative stress. Addition of insulin to the patients’ medication significantly lowered mean glucose as well as oxidative stress. However, again no relationship was found between glucose variability and oxidative stress.

Oxidative stress is thought to induce vascular complications, but eventually it is an indirect marker of disease, not a hard outcome. In Chapter 6 we investigated the effect of glucose variability on the development of peripheral and autonomic neuropathy. For this purpose data from the Diabetes Control and Complications Trial (DCCT) were reanalysed. The DCCT was originally designed to assess the effect of intensive vs. conventional glucose lowering treatment on the development of microvascular complications and included 1,441 type 1 diabetes patients. The development of neuropathy was strongly associated with mean glucose but no additional effect of glucose variability was found.

Chapter 7 shows a reanalysis of The Hyperglycaemia and Its Effect After Acute Myocardial Infarction on Cardiovascular Outcomes in Patients With Type 2 Diabetes Mellitus study (HEART2D). This randomised controlled trial assessed the effect of a prandial insulin regimen compared with a basal insulin regimen on future cardiovascular event rates in type 2 diabetes patients after myocardial infarction, thereby specifically lowering glucose variability. Overall glycaemic control was found to be similar in the two groups but no differences in cardiovascular outcomes were seen despite eighteen percent lower glucose variability in the prandial insulin group.

In conclusion, Part I of this thesis does not support a relationship between glucose variability and oxidative stress or diabetic complications. Moreover, specifically lowering glucose variability in type 2 diabetes patients did not result in a reduction in future cardiovascular event rates. Therefore, there are currently insufficient arguments to specifically lower glucose variability in patients with diabetes regarding complication risk, and treatment should continue targeting mean glucose while avoiding hypoglycaemia as much as possible.
Part II
Marked hyperglycaemia has to be avoided in critically ill patients but there is debate on the optimal glucose target. In Chapter 8 we investigated the relationship between mean glucose during intensive care unit (ICU) admission and mortality in surgical as well as medical patients who were treated according to the most recent guidelines. In both cohorts, mean glucose appeared to be related to ICU mortality by a U-shaped curve, and a “safe-range” for mean glucose could be defined between approximately 7.0 and 9.0 mmol/l. These results are in line with the data from the NICE-SUGAR (Normoglycaemia in Intensive Care Evaluation- Survival Using Glucose Algorithm Regulation) trial and suggest that lowering glucose to normoglycaemia is perhaps doing more harm than good.

Continuous glucose monitoring (CGM) could be a useful tool to achieve more time in the glucose target range. We report in Chapter 9 a head-to-head comparison investigating the accuracy and reliability of the Guardian Real-Time (Medtronic Minimed) and the FreeStyle Navigator (Abbott Diabetes Care) CGM system in 60 cardiac surgery patients admitted to the ICU after surgery. The FreeStyle Navigator performed significantly better in accuracy as well as reliability compared to the Guardian Real-Time. Remarkably, accuracy of both systems was quite good compared to known data for outpatients. These data support the use of the FreeStyle Navigator in cardiac surgery patients. Whether the use of CGM truly increases the time spent in the target range and lowers the incidence of hypoglycaemia should be subject of further study.

We hypothesised that the accuracy of the CGM systems could be influenced by the microcirculation. In Chapter 10 the microcirculation and its effect on CGM accuracy was investigated in the same 60 patients after cardiac surgery. Impairment in microcirculatory parameters was found during the first hours of ICU admission during a median follow-up of 23 hours, but this impairment was not related to CGM accuracy. A decrease in peripheral temperature did decrease the accuracy of the two systems, and an increase in age of the patient as well as an increase in severity of disease influenced the accuracy of the FreeStyle Navigator in a negative way. Further studies need to assess the influence of more profound microcirculatory changes on sensor accuracy in more severely ill patients.

Challenging it is when acute meets chronic hyperglycaemia: the critically ill patient with diabetes. Chapter 11 gives an overview of the current literature on morbidity and mortality in ICU patients with diabetes with special consideration to glucose regulation, insulin treatment and hypoglycaemia. Diabetes is considered to be a risk factor for the development of complications while admitted in the ICU but this does not seem to translate directly into higher mortality. The relation between diabetes and mortality is further investigated in Chapter 12. Hyperglycaemia is common in critically ill patients with diabetes and associated with mortality when above 11.1 mmol/l, but there is...
summary and future considerations

Discussion about the detrimental effect of hyperglycaemia lower than 11.1 mmol/l. Also, intensive insulin therapy seems not beneficial as compared with moderate glycaemic control. Interestingly, at any given level of hyperglycaemia mortality rates are higher in non-diabetic patients compared with diabetic patients, but in the lower glucose range it is the other way round. Patients with diabetes are also vulnerable for developing hypoglycaemic events which are strongly associated with mortality. We recommend to maintain glucose levels between 7.5 and 10.0 mmol/l in critically ill patients with diabetes while avoiding hypoglycaemia as well as extreme hyperglycaemia.

Finally, in Chapter 12 the results of a systematic review and meta-analysis are shown assessing the effect of diabetes on mortality in different ICU types. In total, 141 studies were included containing over 12.4 million patients, including 2.7 million (21.7%) deaths and 2.3 million (18.6%) patients with diabetes. The meta-analysis showed that patients with diabetes who are admitted at the medical, mixed and trauma ICU have similar chances of survival compared to patients without diabetes. Diabetes significantly increased mortality risk only in patients admitted after cardiac surgery, where it distinctly influences the underlying coronary disease. Further studies are needed to unravel the pathophysiological mechanisms by which patients with diabetes seem to be protected in non-surgical settings, despite encountering higher complication rates.

From a clinical perspective, we may conclude from the findings described in Part II of this thesis that the optimal glucose target range in critically ill patients lies above the range considered normoglycaemic, irrespective of the diabetic status prior to admission. Marked hyperglycaemia and hypoglycaemia should be avoided. Continuous glucose monitoring shows good accuracy in cardiac surgery patients, and its accuracy seem independent from microcirculatory parameters.

Future considerations
As always, also this research raises new questions. A decrease in glucose variability seems not to decrease cardiovascular event rates in type 2 diabetes patients after myocardial infarction, but a randomised controlled trial specifically lowering glucose variability in other patient groups has not been performed yet. The most promising results are to be expected in the critically ill because epidemiological studies consistently show that in this population glucose variability is associated with mortality. It will be a major challenge to come up with an intervention in this population that lowers glucose variability while leaving mean glucose unaffected, but it is the only way to investigate whether glucose variability is causally related to mortality or only a manifestation of severe disease. Continuous glucose monitoring might be a useful tool to increase time in target range and decrease hypoglycaemia and perhaps also glucose variability in the critically ill. A randomised controlled trial comparing the FreeStyle Navigator CGM system with point-
of-care glucose measurements assessing these questions is currently being performed in a mixed population of critically ill patients and the results of this trial are avidly waited for. In addition to subcutaneous glucose monitoring, also intra-vascular glucose monitoring devices are being developed with promising results regarding accuracy. However, clinical trails will have to demonstrate that the possible beneficial effects will counterbalance the costs and possible complications of its invasiveness. Finally, an intriguing question is why critically ill patients with diabetes are less affected by hyperglycaemia than patients without previously diagnosed diabetes, while hypoglycaemia seems more harmful.

Conclusion
The central question of this thesis is whether it is necessary to curb all glucose peaks. From the studies presented in this thesis we conclude that this is not always the case. In diabetes it is important to lower mean glucose while avoiding hypoglycaemia, but we found that lowering of glucose to normoglycaemia in critically ill patients seems actually harmful, in patients with and without diabetes. In addition, our studies show that glucose variability does not need separate treatment in diabetes, while it is associated with mortality in critically ill patients without diabetes. Thus, not all what goes up must come down.