Glycemic control in acute stroke: ‘balancing the risks’
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Patients admitted with acute ischemic stroke or acute aneurysmal subarachnoid hemorrhage (SAH) often have increased levels of blood glucose on admission and throughout the clinical course. These high blood glucose levels, especially if persistent, appear to be strong and independent predictors of worse clinical outcome. Several pathophysiological mechanisms could account for a detrimental effect of hyperglycemia on clinical outcome. Clinical trials in critically ill patients with conditions other than stroke have shown a beneficial effect of glucose-lowering therapy. Therefore, patients with acute ischemic stroke and patients with aneurysmal SAH might also potentially benefit from glucose-lowering therapy. This thesis, which is part of the Glucose Lowering in Acute Stroke Study (GLASS) project, consists of studies that deal with hyperglycemia and its treatment control in patients with acute ischemic stroke. The research presented concerns the association between glucose metabolism and various measures of clinical outcome, the improvement of glycemic control in terms of safety and efficacy and assessment of the current evidence on glucose-lowering therapy in stroke patients.

In the FIRST PART of this thesis that deals with hyperglycemia and its treatment control in patients with acute ischemic stroke, chapter 2 reviews the available evidence linking hyperglycemia to a poor clinical outcome in patients with ischemic stroke. We highlighted the pathophysiological mechanisms that might underlie the deleterious effects of hyperglycemia on acute stroke prognosis and we systematically reviewed the literature concerning tight glycemic control after stroke. The most important finding is that establishing glycemic control in ischemic stroke patients is very challenging in terms of efficacy and safety. Hence, more phase two studies are essential before a large scale RCT is initiated to investigate the clinical benefit of glycemic control.

For a RCT, surrogate endpoints for clinical outcome could be helpful. In chapter 3 we investigated if cognitive outcome could serve as such a surrogate endpoint for clinical outcome. The findings of a cohort study including 113 first ever ischemic stroke patients are described. Patients were subjected to a neuropsychological examination in the acute phase and after six months follow-up. The cohort was dichotomized into patients with glucose levels above (hyperglycemia) or below 7.0 mmol/L. We did not find an association between hyperglycemia and impaired cognitive outcome after six months. Therefore, cognition appears to be less feasible as a surrogate outcome measure for a future trial. In the same study, we confirmed that hyperglycemia predicts poor clinical outcome in patients with cortical stroke— but not in subcortical stroke, emphasizing that care should be taken in selecting patients for a future trial. In Chapters 4 and 5, we describe two small multicenter studies that investigated different treatment regimes to control hyperglycemia in ischemic stroke patients. In the first study, ischemic stroke patients with hyperglycemia on admission were randomized to receive conventional treatment, strict glycemic control with intravenous insulin or strict glycemic control with subcutaneous meal related insulin. In addition, a group of ischemic stroke patients with a glucose level below 7.0 mmol/L on admission served as controls. The results were somewhat disappointing as neither of the regimes resulted in lower glucose profiles compared to controls, while treatment was associated with increased hypoglycemia. The main reason for the persistently high blood glucose levels were the occurrences of postprandial hyperglycemic episodes. Therefore in the subsequent study we subjected patients to continuous tube feeding in addition to intravenous
In addition, we designed a web-based computerized treatment algorithm to assist the nursing staff in the execution of the protocol. With this regime, we managed to improve glycemic control substantially, maintaining blood glucose levels within a low physiological range (4.4 to 6.1) for five consecutive days. However, the intensive protocol also demanded that non-dysphagic patients had to be subjected to continuous tube feeding and that glucose levels had to be checked frequently with fingerpicks. Discomfort caused by the latter led to the withdrawal of informed consent of one patient. A more important drawback of the study was that glucose lowering was associated with hypoglycemic (glucose <3.0 mmol/L) episodes in 20% of patients, although no serious (glucose <2.2 mmol/L) hypoglycemic episodes were recorded. Currently we are randomizing patients in a trial that investigates if vildagliptin (a dipeptidyl peptidase-4 inhibitor) can reduce the number of hypoglycemic episodes when administered as an add-on to intravenous insulin.

The second part of this thesis concerns hyperglycemia in aneurysmal SAH. Chapter six is a systematic review and meta-analysis. We found that 69% of aneurysmal SAH patients have hyperglycemia on admission with a mean glucose of 9.3 mmol/L (range, 7.4 to 10.9 mmol/L). The pooled odds ratio for poor outcome associated with hyperglycemia was 3.1 (95% CI, 2.3 to 4.3). Interestingly, this relation persisted when studies were grouped with a high- or low median cut-off to define hyperglycemia, indicating that glucose levels relate to poor clinical outcome independent of the cut-off used to define hyperglycemia. In chapter seven we sought to delineate the association between abnormalities of glucose metabolism and outcome in aneurysmal SAH patients. First we assessed if the relation between high levels of admission blood glucose and poor outcome would be independent of other baseline characteristics known to predict poor clinical outcome. Second, as mean fasting glucose levels within the first week are a more accurate reflection of glucose metabolism than single admission blood glucose levels, we also assessed the association between mean fasting glucose levels with clinical outcome. Finally, as high blood glucose levels have been associated with the occurrence of delayed cerebral ischemia (DCI), we assessed whether the association between glucose levels and outcome was mediated by the occurrence of DCI. We studied 265 consecutive aneurysmal SAH patients and confirmed an association between admission blood glucose levels with DCI and poor outcome, but these associations were not independent from other baseline predictors of poor clinical outcome such as severity of the aneurysmal SAH. However, the association between high mean fasting glucose levels with DCI and poor outcome were much stronger and remained after adjusting for other baseline predictors of poor outcome. The association between mean fasting glucose levels and poor outcome remained essentially the same after adjusting for DCI occurrence, indicating that DCI is not the major determinant in the association between high fasting glucose and poor clinical outcome.

In chapter eight we describe the result of a laboratory study that aimed to prospectively study disturbances of glucose metabolism inflicted by acute aneurysmal SAH upon patients without known abnormalities of glucose metabolism. In addition we explored possible correlations with markers of stress. We included thirteen consecutive aneurysmal SAH patients not known to have abnormalities of glucose metabolism. Blood samples were drawn in fasting conditions during the first three weeks after the aneurysmal SAH and we assessed measures of glucose metabolism such as fasting glucose, insulin and free fatty acids (FFA). With the Homeostatic model Assessment (HOMA) we constructed indices of pancreatic β-cell function and insulin
resistance. In addition, patients were subjected to an oral glucose tolerance tests (OGTT) during the clinical course and after three months to assess glucose tolerance. We found that during the first days after the ictus an acute pancreatic β-cell dysfunction with relative hypoinsulinemia appears to play an important role as the underlying cause of hyperglycemia. Later this is also accompanied by increased insulin resistance. Pancreatic β-cell dysfunction was also associated with increased levels of cortisol, indicating that the stress reaction inflicted by the SAH is involved in β-cell dysfunction and the development of hyperglycemia. The results from the OGTT showed transient abnormalities of glucose tolerance during the clinical course. The finding that pancreatic β-cell dysfunction plays an important role as the underlying cause of hyperglycemia is interesting as it is generally assumed that insulin resistance is the major factor leading to hyperglycemia in critically ill patients. In Chapter nine we have reviewed the mechanisms involved in the pathophysiology of hyperglycemia in aneurysmal SAH patients and we discuss how hyperglycemia may contribute to poor clinical outcome in this patient group. In addition, we performed a systematic literature search on glucose-lowering treatment in aneurysmal SAH patients. We conclude that currently there is no evidence that hyperglycemia in aneurysmal SAH patients should be lowered actively and that glucose-lowering treatment is accompanied by an increase in hypoglycemic episodes raising concerns about the safety of this therapy.