Glycemic control in acute stroke: ‘balancing the risks’
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Citation for published version (APA):

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PANCREATIC BETA CELL DYSFUNCTION AND INSULIN RESISTANCE AFTER SUBARACHNOID HEMORRHAGE

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ABSTRACT

Background
Hyperglycemia is a common finding and an independent risk factor for increased morbidity and mortality in aneurysmal subarachnoid hemorrhage (SAH). Although in these patients hyperglycemia is commonly ascribed to insulin resistance, there is little understanding of underlying mechanisms.

Aims
To prospectively study temporal disturbances of glucose metabolism after aneurysmal SAH in patients without known abnormalities of glucose metabolism and to explore possible correlations with markers of stress.

Methods
In consecutive aneurysmal SAH patients not subjected to insulin therapy, in-hospital and follow-up oral glucose tolerance tests (OGTT) and assessments of insulin resistance, pancreatic β-cell function, free fatty acids (FFA) and cortisol were performed and compared with reference values.

Results
We included 13 patients. In the first two weeks of admission, median fasting glucose and FFA levels were elevated while insulin levels were not. OGTT tests were indicative of glucose intolerance in all patients at days 3 and 7, while on follow-up one patient had glucose intolerance and all patients had normal fasting glucose levels. Pancreatic β-cell function was impaired throughout the first week and insulin resistance appeared from day 4 to 10. Levels of cortisol correlated with higher fasting glucose and increased FFA. FFA in turn correlated with pancreatic β-cell dysfunction.

Conclusions
aneurysmal SAH patients have transient abnormalities of glucose metabolism. In the first week after the ictus this appears to result predominantly from transient pancreatic β-cell dysfunction, and later also from insulin resistance.
INTRODUCTION

Hyperglycemia occurs frequently after aneurysmal SAH (SAH) and is an independent risk factor for increased morbidity and mortality.\textsuperscript{204,218,254} Lowering of blood glucose levels appears beneficial for various groups of critically ill patients,\textsuperscript{6,7,29,30,255} and as such is a potential focus for future treatment for aneurysmal SAH patients.\textsuperscript{124} Nevertheless, the benefit of such treatment still remains to be proven in this patient group. Moreover, in patients with aneurysmal SAH, effective lowering of blood glucose levels with insulin is not easy to accomplish. Especially the increased occurrence of hypoglycemic episodes with the potential for negative outcomes remains a concern.\textsuperscript{8,24} Insight into the mechanisms that cause hyperglycemia in aneurysmal SAH patients could provide directions for further studies into the safety and efficacy of glucose-lowering treatment in these patients. One hypothesis is that the observed hyperglycemia in SAH is caused by stress: so called stress hyperglycemia. The mechanisms leading to stress hyperglycemia have been studied in several critical illnesses, but little is known of this topic for aneurysmal SAH patients. In general, the development of stress hyperglycemia is thought to be the result of insulin resistance inflicted by hormonal and inflammatory responses imposed by the acute illness. Increased stress hormones counter-regulatory to insulin (e.g. cortisol) as well as an increased inflammatory response with the release of cytokines (e.g. tumor necrosis factor-\textalpha{}), both increase hepatic glucose production and suppress glucose uptake into skeletal muscle, with consequent hyperglycemia.\textsuperscript{4,256-260} Another factor that could contribute to hyperglycemia in acute illness is the unveiling of pre-existent insulin resistance. For example, a substantial portion of patients with acute ischemic stroke or myocardial infarction appear to have unrecognized insulin resistance prior to the event.\textsuperscript{36-38,261} Whether this also contributes to hyperglycemia in patients with acute aneurysmal SAH is uncertain.

The aim of this study was to examine temporal disturbances of glucose metabolism after aneurysmal SAH in patients without known abnormalities of glucose metabolism prior to the event. In addition, we explored the association between glucose metabolism and markers of stress.

METHODS

PATIENTS

In this prospective study, we included consecutive adult (18 years or older) patients presenting within 24 hours after onset of aneurysmal SAH with confirmatory evidence of a ruptured aneurysm on imaging, that were admitted to the Academic Medical Centre (Amsterdam, the Netherlands). Exclusion criteria were: (1) known diabetes mellitus (DM) or glycosylated hemoglobin (HbA1C) exceeding 6.5 \%; (2) patients treated with insulin (i.e. all patients with admission glucose levels exceeding 12.0 mmol/L and all patients that were admitted to the intensive care unit (ICU); (3) active liver disease (liver alanine aminotransferase, or aspartate aminotransferase more than three times the upper limit of normal); (4) renal insufficiency (defined as serum creatinine more than twice the upper limit of normal, or patients requiring dialysis); (5) pregnancy or lactation, and (5) imminent death. Written informed consent was obtained from all patients or their relatives.
LABORATORY MEASURES
Except for admission blood samples, all samples were drawn following an overnight fast, between 7:30 and 8:00 AM. Samples were immediately centrifuged and stored at -20 °C. Day zero was defined as the day the aneurysmal SAH occurred with day one as the first morning after aneurysmal SAH onset. Samples were drawn daily on days one to seven and on days 10, 14, and 17. The following measures of glucose metabolism were obtained: HbA1C (day one only); fasting glucose, fasting insulin, free fatty acids (FFA) and glucagon. Paired fasting glucose and fasting insulin were used to calculate HOmeostatic Model Assessment (HOMA) indices. These indices are derived from a computer model that consists of a number of nonlinear empirical equations describing the functions of organs and tissues involved in glucose regulation. The indices reflect insulin resistance and pancreatic β-cell function. The output of the model is calibrated to give a normal insulin resistance (HOMA-IR) of 1 and a normal β-cell function (HOMA-β) of 100%. The model has been evaluated in healthy subjects as well as in patients suffering from various diseases, and performs well in comparison with several tests of insulin sensitivity and pancreatic β-cell function. In a cohort study in a large population with no previous evidence of DM, HOMA-IR exceeding 1.21 corresponded with insulin resistance defined by an OGTT. Serum cortisol and adrenocorticotropic hormone (ACTH) were assessed as markers of stress.

ORAL GLUCOSE TOLERANCE TEST (OGTT)
Patients were subjected to an oral glucose tolerance test (OGTT) on days three and seven of admission and during follow-up after three months. This test involves the ingestion within five minutes of an oral solution with 75 mg of glucose diluted in 300 ml water, after an overnight fast. Capillary blood glucose levels are assessed immediately before ingestion (T=0), and at one (T=1) and two (T=2) hours thereafter. During non-stress conditions a capillary glucose level exceeding 7.8 mmol/L at T=2 is considered diagnostic of DM.

OUTCOME ASSESSMENT AND STATISTICAL ANALYSIS.
Normally distributed baseline data are expressed as a mean with standard deviation. Because of the relatively small sample size and possible skewed distribution of the data, all outcome data are depicted as median levels and the corresponding interquartile ranges [IQR]. Levels of laboratory measurements were compared with laboratory reference levels. To compare the OGTTs during the clinical course with the OGTTs during follow-up, we used the two tailed Wilcoxon signed-rank test to compare the capillary T=2 glucose levels. We used two tailed Spearman’s correlation coefficients to explore a possible correlation between measures of glucose metabolism and measurements of the stress response and FFA levels during the first ten days.

RESULTS
Fifteen patients were initially included, but two patients had to be excluded; one patient had to be transferred to the ICU immediately after admission and one patient appeared to have an increased HbA1C. Therefore, 13 patients were available for analysis. Baseline characteristics are depicted in table 1. As patients with poor grade aneurysmal SAH were excluded because of ICU admission, patients were in a relatively good clinical condition (median World Federation
of Neurological Surgeons Scale 1). In nine patients (70%), the ruptured aneurysm was treated with endovascular coiling; the other patients were surgically clipped. One patient was treated on day zero, ten patients on day one and the two remaining patients on day two. Blood samples could not be obtained on each day for all patients. Reasons for this were, failure to centrifuge and store sufficient samples, or because the patient was transferred back to the referring hospital before completion of the study. Blood samples were obtained from at least ten patients on days one to seven; from nine on day ten, and from seven on days 14 and 17. Serial measurements of fasting glucose, fasting insulin, HOMA indices and FFA are depicted in figures A-E. Median fasting glucose levels exceeded reference level (5.6 mmol/L) on days 1 to 10. On the first day, all fasting glucose measurements exceeded reference levels, but during the subsequent nine days the proportion of patients with normal fasting glucose levels increased (e.g. 50% on day 7). After 3 months, median capillary fasting glucose levels were normal [5.2; IQR: 4.9 to 5.5 mmol/L]. Median insulin and individual levels of insulin did not exceed reference level (<172 pmol/L) on any of the days. Median HOMA-IR indices were slightly increased on the first days and from day 4 to 7, returning to normal on day 17. Median HOMA-B indices indicated β-cell dysfunction from the first day with steady improvement throughout the first week and near normalization at the end of the third week. During the first three days, all individual FFA measurements exceeded reference level (0.44 mmol/L) and then slowly declined. During the first week, day 3 OGTT could be performed in nine patients and day 7 OGTT was available for eight patients. In all but one patient OGTT was performed at follow-up. Fasting and two hour capillary glucose assessments from the OGTTs are depicted in figure F. On the OGTTs of day 3 and day 7 all patients had two hour post glucose load capillary glucose levels exceeding 7.8 mmol/L indicating impaired glucose tolerance. Conversely, at follow-up only, only one patient showed impaired glucose tolerance, indicating that the impairment of glucose tolerance during the clinical course was transient. Increased levels of fasting glucose correlated with higher fasting

Table 1 | Baseline characteristics.

<table>
<thead>
<tr>
<th>Variable</th>
<th>(N=13)</th>
</tr>
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<tbody>
<tr>
<td>Mean age (years ± sd)</td>
<td>52 ± 6.4</td>
</tr>
<tr>
<td>Male (%)</td>
<td>2(14)</td>
</tr>
<tr>
<td>Hypertension (%)</td>
<td>2(14)</td>
</tr>
<tr>
<td>Hypercholesterolemia (%)</td>
<td>1(7)</td>
</tr>
<tr>
<td>Mean admission glucose (mmol/L ± sd)</td>
<td>8.2 ± 1.9</td>
</tr>
<tr>
<td>HbA1C % day 1 ( ± sd)</td>
<td>5.7 ± 0.3</td>
</tr>
<tr>
<td>Admission</td>
<td></td>
</tr>
<tr>
<td>Median WFNS scale [range]</td>
<td>1 [1-3]</td>
</tr>
<tr>
<td>Mean MAP (mmHG ± sd)</td>
<td>113 ± 27</td>
</tr>
<tr>
<td>Mean BMI ± sd</td>
<td></td>
</tr>
<tr>
<td>on admission</td>
<td>24.3 ± 3.9</td>
</tr>
<tr>
<td>at follow-up</td>
<td>25.1 ± 4.4</td>
</tr>
</tbody>
</table>

sd: standard deviation; HbA1C: Glycosylated hemoglobin; WFNS: World Federation of Neurological Surgeons; MAP: Mean Arterial Pressure; BMI: Body Mass Index.
Figures | A-E: median serial measurements of parameters of glucose metabolism; F: Fasting and two hour capillary glucose assessments from the oral glucose tolerance tests.

Bars indicate upper and lower limit; SAH = aneurysmal subarachnoid hemorrhage; HOMA = HOmeostatic Model Assessment; IR=Insulin Resistance; B = pancreatic β-cell function; OGTT: Oral Glucose Tolerance Test; T=0: pre-glucose load fasting glucose; T=2: two hour post-glucose glucose; dotted line: upper limit of normal.
Table 2 | Correlation between parameters of glucose metabolism and stress.

<table>
<thead>
<tr>
<th></th>
<th>Fasting glucose</th>
<th>Fasting insulin</th>
<th>HOMA IR</th>
<th>HOMA B</th>
<th>Free Fatty Acids</th>
<th>Cortisol</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fasting glucose</td>
<td>X</td>
<td>0.34***</td>
<td>-0.41**</td>
<td>0.40**</td>
<td>0.20***</td>
<td>0.4**</td>
</tr>
<tr>
<td>Fasting insulin</td>
<td>0.34**</td>
<td>X</td>
<td>0.99</td>
<td>0.66</td>
<td>0.20***</td>
<td>0.07</td>
</tr>
<tr>
<td>HOMA IR</td>
<td>-0.41**</td>
<td>0.99</td>
<td>X</td>
<td>0.6</td>
<td>-0.05</td>
<td>0.09</td>
</tr>
<tr>
<td>HOMA B</td>
<td>0.40**</td>
<td>0.66</td>
<td>0.6</td>
<td>X</td>
<td>0.30**</td>
<td>-0.20***</td>
</tr>
<tr>
<td>Free Fatty Acids</td>
<td>0.20***</td>
<td>-0.20***</td>
<td>-0.05</td>
<td>-0.30**</td>
<td>X</td>
<td>0.3*</td>
</tr>
<tr>
<td>Cortisol</td>
<td>0.4**</td>
<td>0.07</td>
<td>0.09</td>
<td>-0.2</td>
<td>***</td>
<td>X</td>
</tr>
</tbody>
</table>

Two tailed Spearman’s correlation coefficients (rho) between parameters of glucose metabolism and stress throughout the first ten days of admission; HOMA: HOmeostatic Model Assessment; IR: Insulin resistance; B: β-cell function; *: p<0.05; **: P<0.01; ***: p<0.001.

insulin levels (rho: 0.34; p<0.01), with lower indices of β-cell function (rho: -0.41; p<0.00) and with higher indices of insulin resistance (rho: 0.40; p<0.00) (Table 2). FFA levels correlated with lower indices of β-cell function (rho: -0.3; p<0.01) and a trend was seen towards a correlation between higher FFA levels and lower fasting insulin levels (rho: -0.2; p<0.1). Median levels of glucagon, cortisol and ACTH were not elevated on any of the days (data not shown). During the first ten days, higher cortisol levels correlated with higher fasting glucose levels (rho: 0.4; p<0.01) and with higher FFA levels (rho: 0.3; p<0.05). A trend was seen towards a correlation between higher cortisol levels and lower indices of β-cell function (rho: -0.2; p<0.1). We did not find a correlation between BMI with HOMA indices or with OGTTs.

DISCUSSION

The results of our study indicate that in patients with aneurysmal SAH without known abnormalities of glucose metabolism, aneurysmal SAH inflicts an acute dysfunction of pancreatic β-cells with recovery over two weeks. Insulin resistance on the other hand seems to develop later, during the second half of the first week with recovery by day ten. In addition, the post aneurysmal SAH glucose intolerance was normalized at 3 months follow-up. The finding that there is a transient impaired glucose tolerance is patients with aneurysmal SAH is in line with a previous study and suggests that hyperglycemia during the clinical course of aneurysmal SAH is not the result of previously undiscovered impairments of glucose metabolism.271 Although the number of patients are too small to draw a definite conclusion, this view is supported by the observation that DM or other abnormalities known to be associated with disturbances of glucose metabolism such as increased body mass index and hypercholesterolemia are not considered risk factors for aneurysmal SAH.196;236 Hyperglycemia after aneurysmal SAH could result from so called stress hyperglycemia. In general, it is thought that the two primary mechanisms responsible for stress hyperglycemia in acutely ill patients are enhanced hepatic glucose production and increased insulin resistance.4,45,257,272 The role of pancreatic β-cell function in response to critical illness appears less well studied, although several studies in the 1970s and 1980s indicate β-cell dysfunction in critically ill patients.273-275 Moreover, it was recently reported that primary β-cell dysfunction is the main cause of hyperglycemia in
critically ill children with respiratory and cardiovascular failure. Experimental studies have shown that stress hormones can suppress insulin secretion in pancreatic β-cells. Recently we reported that higher cortisol levels correlate with increased random glucose levels in aneurysmal SAH patients. In the present study, higher levels of cortisol were also correlated with higher levels of fasting glucose, and a trend was seen for a correlation between higher levels of cortisol and β-cell dysfunction. We also found increased levels of FFA as compared to reference levels. This is consistent with increased lipolysis due to hypoinsulinemia, but could also be explained by the increased stress response as higher cortisol levels correlated with higher FFA levels and, in general, an increased stress reaction is accompanied by lipolysis with a subsequent increase in FFA levels. Previous studies reported similar observations, with increased FFA levels in cerebral spinal fluid of patients with aneurysmal SAH or with traumatic brain injury. The association between FFA and insulin appears to be complex. In healthy volunteers, acute infusion of FFA was associated with increased insulin levels, whereas in subjects with impaired glucose tolerance, elevation of plasma FFA levels for 24 hours inhibited insulin secretion.

The results of the present study should be interpreted with some caution. A limitation is that the sample size was small and that we did not have a control group. Moreover, the studied population concerns a subset of aneurysmal SAH patients with a relatively good clinical condition. We did not include more severe patients that were admitted to the ICU, since these patients are routinely subjected to insulin in modern ICU care. However, we expect that with clinically more severe aneurysmal SAH these findings will be even more robust as abnormalities of glucose metabolism are more pronounced in this subset of patients. We conclude that patients with acute good grade aneurysmal SAH experience transient abnormalities of glucose tolerance. In these patients initially an acute pancreatic β-cell dysfunction with relative hypo-insulinemia appears to play an important role as the underlying cause of hyperglycemia, which later on is accompanied by insulin resistance. The results of this study should be regarded primarily as hypothesis generating as the sample size was too small to draw firm conclusions. If our results can be confirmed in future studies, the next step would be to elucidate how β-cell dysfunction emerges, for example whether this results from pure loss of β-cell mass, direct inhibition of insulin secretion or deficient signaling pathways. Finally therapy specifically aimed at restoration of β-cell dysfunction could be of value in the treatment of hyperglycemia in aneurysmal SAH patients.