Body Mass Index and Leptin Levels in Serum and Cerebrospinal Fluid in Relation to Delayed Cerebral Ischemia and Outcome after Aneurysmal Subarachnoid Hemorrhage

Michael Veldeman
Miriam Weiss
Tim Philipp Simon
Anke Hoellig
Hans Clusmann
Walid Albanna (walidalbanna@yahoo.de)

https://orcid.org/0000-0001-9986-8739

Research Article

Keywords: Subarachnoid hemorrhage, delayed cerebral ischemia, leptin, body mass index, fat metabolism

DOI: https://doi.org/10.21203/rs.3.rs-190557/v1

License: This work is licensed under a Creative Commons Attribution 4.0 International License.
Read Full License
Abstract

Objective

Aneurysmal subarachnoid hemorrhage (SAH) is associated with a high mortality rate and may leave surviving patients severely disabled. After the initial hemorrhage, clinical outcome is further compromised by the occurrence of delayed cerebral ischemia (DCI). Overweight and obesity have previously been associated with protective effects in the post-bleeding phase. The aim of this study was to assess the effects of patient’s body mass index (BMI) and leptin levels on the occurrence of DCI, DCI-related cerebral infarction and clinical outcome.

METHODS

263 SAH patients were included of which leptin levels were assessed in 24 cases. BMI was recorded along disease severity documented by the Hunt and Hess and modified Fisher scales. The occurrence of clinical or functional DCI (neuromonitoring, CT Perfusion) was assessed. Long-term clinical outcome was documented after 12 months (extended Glasgow outcome scale).

RESULTS

A total of 136 (51.7%) patients developed DCI of which 72 (27.4%) developed DCI-related cerebral infarctions. No association between BMI and DCI occurrence ($P = .410$) or better clinical outcome ($P = .643$) was identified. Early leptin concentration in serum ($P = .258$) and CSF ($P = .159$) showed no predictive value in identifying patients at risk of unfavorable outcome. However, a significant increase of leptin levels in CSF occurred from 326.0 pg/ml IQR 171.9 prior to DCI development to 579.2 pg/ml IQR 211.9 during ongoing DCI ($P = .049$).

CONCLUSIONS

In our data, no association between obesity and clinical outcome was detected. After DCI-development, leptin levels in CSF increased either by an upsurge of active transport or disruption of the blood-CSF barrier.

Trial registration: This trial has been registered at ClinicalTrials.gov (NCT02142166) as part of a larger scale prospective data collection. BioSAB: https://clinicaltrials.gov/ct2/show/NCT02142166

Introduction

Aneurysmal subarachnoid hemorrhage (SAH) remains a devastating disease affecting around 9 / 100.000 people each year [8]. After SAH, the main predictors of outcome are the initial clinical grade either defined by the Hunt and Hess (H&H) or WFNS scale and the amount of subarachnoid blood load stratified according to the modified Fisher scale (mFisher) [34, 7]. Despite general advancements in critical care management for SAH patients, outcome in those with higher clinical grade or blood load
remains poor [25, 9]. The initial aneurysm rupture results in a steep increase of intracranial pressure and resulting sudden drop in cerebral perfusion pressure [26]. It is currently assumed that this initial increase in intracranial pressure and consecutive drop in cerebral perfusion pressure has irreversibly initiated a deleterious cascade coined with the umbrella term early brain injury.

During the first two weeks post-hemorrhage, patients remain susceptible to ischemic strokes in which cerebral vasospasm plays an undisputed role alongside many other contributing factors [35]. This delayed cerebral ischemia (DCI) can eventually result in cerebral infarctions, further compromising long-term clinical outcome [36].

Obesity is an established risk factor for cardio- and cerebrovascular disease, surgical complications and nosocomial infections [2]. Contrary to this association, there is an “obesity paradox” where an increased body mass index (BMI) was associated with an overall lower mortality and complication rate, after ischemic stroke [31, 19] and intracerebral hemorrhage [5, 18]. SAH patients suffering from obesity do not fare worse or may even profit from obesity by unknown mechanisms in regard to DCI-development, clinical outcome, and overall rate of complications [24, 33, 6]. A single trial in SAH patients described a lower risk of DCI and DCI-related infarction associated with elevated BMI [29]. Nonetheless, the results of a systemic review addressing this obesity paradox in SAH remained inconclusive as most trials suffered restrictions in design, resulting in limited external validity [27].

Leptin, initially discovered as a regulator of food intake and energy expenditure, is emerging as a pleiotropic molecule involved in various physiological and pathological conditions [15, 13]. Under normal physiological circumstances, this peptide has an inhibitory effect on appetite via its modulation of the hypothalamic satiety center. Leptin is, however, also part of a broader neuronal circuit regulating weight and governing energy homeostasis. Crossing the blood-brain barrier, leptin acts on receptors within the central nervous system and exerts an anti-apoptotic effect, increases neuronal survival, and can induce neurogenesis as well as angiogenesis [21]. As part of the cytokine superfamily, leptin has structural and functional similarities with pro-inflammatory cytokines such as Interleukin-1, -6, and −12, hence the name adipokine. Furthermore, the leptin receptor (OB-R) is related to class I cytokine receptors, including a common signal-transducing component from the IL-6-related family of cytokines [3]. In obesity, leptin resistance develops, leading to an inability to detect satiety despite sufficient available energy stores. Serum leptin concentrations correlate positively with the percentage of body fat, illustrating the insensitivity of most people suffering from obesity, to endogenous leptin production [4]. This makes leptin an interesting target to assess body fat content's effects on DCI-occurrence and long-term outcome after SAH.

In this study we set out to assess the obesity paradox in a prospective SAH data collection, based on BMI but also on levels of leptin in cerebrospinal fluid (CSF) and serum, the latter as surrogate markers of body fat mass.

Methods
Patient population and study design

Patients with aneurysmal subarachnoid hemorrhage presenting at our institution between 2010 and 2018 were screened for eligibility. This observational data collection was approved by the local ethics committee (EK 062/14) and the trial was retrospectively registered (NCT02142166). Patients were included in case of confirmed aneurysm rupture on CT- or conventional angiography, aged ≥ 18 years. Patients were excluded in case of foreseeable early mortality due to direct brain stem injury (on imaging or uni-/bilateral fixed pupils). Basic demographic data alongside BMI were recorded for each patient on admission based on weight (kg) and height (meters). BMI was categorized according the WHO criteria with the addition of an obesity subdivision resulting in five categories: underweight (< 18.5 kg/m²), normal weight (≥ 18.5 to < 25 kg/m²), overweight (≥ 25 to < 30 kg/m²), obesity grade 1 (≥ 30 to < 35 kg/m²) and obesity grade 2 (≥ 35 kg/m²). This subdivision was added to allow a more precise risk stratification. Initial clinical grade based on the Hunt & Hess grading scale and the amount of subarachnoid blood on CT scanning according to the modified Fisher scale were noted. Additionally, length of ICU stay and of ventilation were documented for each patient.

Cerebral infarctions diagnosed during DCI (as defined below) or as a first sign of ongoing DCI, were registered as DCI-related infarction. Embolic stroke due to halted anticoagulation in patients with cardiac arrhythmias or as a result of surgical or endovascular aneurysm treatment or endovascular DCI rescue treatment, was identified based on history and presentation on imaging and excluded. Cases in which multiple DCI-related infarctions triggered withdrawal of technical life-support were labelled as DCI-related mortality. Clinical outcome was assessed by the extended Glasgow Outcome Scale (GOSE) after 12 months by an independent assessor via a structured telephone interview with the patient, his or her next-of-kin or caretaker. Patients were excluded in case of missing long-term outcome data.

Patient management

All patients were treated according to a standardized treatment protocol consistent over the inclusion period. Aneurysms were secured via endovascular coiling or surgical clipping within 48 hours after admission, after which patients were monitored in a neurosurgical intensive care unit. All patients were routinely treated with oral nimodipine in a 6 x 60 mg/d dose. DCI occurrence was either determined by clinical deterioration not attributable to other causes (i.e. hydrocephalus, electrolyte imbalance, seizure, infection etc.) or functional deterioration defined by a new CT perfusion deficit. Oxygenation (p₂O₂ < 10 mmHg or ≥ 10 mmHg with continuous decrease) or metabolic crisis (lactate / pyruvate ratio ≥ 40 or < 40 with continuous increase) as measured by invasive neuromonitoring probes (Neurovent PTO®, Raumedic®, Helmbrechts, Germany and 71 High Cut-Off Brain Microdialysis Catheter, µdialysis®, Stockholm, Sweden) were indicators to perform CT Perfusion imaging. First tier treatment was initiated after diagnosis of DCI and consisted of induced euvolemic arterial hypertension (≥ 180 mmHg) by means of intravenous noradrenaline infusion. In refractory cases, second tier endovascular rescue treatment was considered by either transluminal balloon-angioplasty or continuous intra-arterial
spasmolysis [40]. Nutrition was administered according to the guidelines by the European Society for Clinical Nutrition and Metabolism (ESPEN) for ICU patients [32].

Data collection and subgroup analyses

From patients treated between 2014 and 2016, a sample subgroup of 24 patients was selected and included to be representative for the entire cohort based on age, gender, H&H and mFisher, with the added prerequisite of having an external ventricular drainage (EVD) in place for cerebrospinal fluid (CSF) collection. Leptin levels were determined in serum and CSF samples during three, a priori defined sampling periods: early (d0−3), pre-DCI (measurement 2–4 days prior to DCI diagnosis) and during ongoing DCI. Systemic (ng/ml) and CSF leptin (pg/ml) levels were collected once in every epoch, for each individual patient, resulting in three sample pairs (serum and CSF) per patient. Sampling was done in the afternoon (between 12:00 and 17:00 PM) together with routine blood drawing and leptin concentrations were measured in CSF and plasma by means of a sandwich enzyme-linked immune-assay (Human Leptin Kit, Meso Scale Discovery®, Rockville, USA).

Pairs of patient subgroups were defined based on dichotomization of the initial Hunt & Hess clinical grading (good grade H&H 1−2 vs. poor grade H&H 3−5), modified Fisher scale (mFisher1−2 vs. mFisher3−4), and clinical outcome (unfavorable: GOSE1−4 vs. favorable: GOSE5−8). Additional subgroups were created based on the occurrence of DCI (noDCI vs. DCI) and DCI-related cerebral infarction (noInfarction vs. Infarction). An analysis of leptin levels before, during and after DCI together with the ratio of leptin CSF to plasma concentration, was conducted.

Outcome definition

The primary endpoint was defined as outcome assessed by the extended Glasgow outcome scale (GOSE) after 12 months. The GOSE was dichotomized as is conventional, into unfavorable (GOSE1−4), and favorable (GOSE5−8) outcome. Additional outcome parameters were the association between BMI or leptin levels and DCI occurrence, the occurrence of refractory DCI (necessitating endovascular treatment), DCI-related infarction, DCI-related mortality, and overall mortality.

Statistical analysis

Descriptive statistics are represented as mean and standard deviation for continuous variables unless non-normally distributed in which case median and interquartile range is provided. Categorical data is depicted as frequencies and percentages. Normality testing was done via plotting and the Shapiro-Wilk test. Parametric continuous data were tested using T-tests and for non-parametric variables using the Mann-Whitney-U test. Paired continuous non-parametric data were analyzed via the Wilcoxon signed ranks test, and categorical data were compared using Pearsons-χ² test. To assess the predictive value of leptin levels on DCI and outcome, a receiver operating characteristics (ROC) analysis with calculation of the Area Under the Curve (AUC) was performed. The presence of a correlation between leptin levels and BMI in this cohort was assessed by a Spearman correlation coefficient. The alpha significant level was set at a two-sided p-value below 0.05, and all statistical analyses were performed using SPSS v. 25 (IBM,
Results

Participants

A total of 305 admitted SAH patients were analyzed for inclusion between 2010–2018. In 37 cases, long-term clinical outcome was missing due to a loss in follow-up. Five patients were excluded because of relevant prior comorbidity. The recruitment process is illustrated in Fig. 1. The mean age of the remaining 263 patients was 53.9 ± 12.7 years with a female to male ratio of 192 (73.0%) to 71 (27.0%). The aneurysm was secured with surgical clipping in 119 (45.2%) patients and via endovascular access in 141 (53.6%) of cases. Three patients received a combination of both occlusion techniques. The median BMI was 24.8 ± 5.4 kg/m^2. Five patients were underweight (1.9%), 133 presented with a normal weight (50.6%), 90 were overweight (34.2%), 25 were classified as obesity grade 1 (9.5%) and 10 as obesity grade 2 (3.8%). No significant differences in outcome relevant baseline characteristics such as H&H and mFisher grading or aneurysm treatment modality were observed between BMI categories. (Suppl. Table 1)

A total of 136 (51.7%) patients developed DCI of which 72 (27.4%) developed DCI-related cerebral infarctions. DCI was the direct cause of death in 27 (10.3%) patients. Favorable outcome was achieved after 12 months in 162 (61.6%) of cases. For the analysis of serum and CSF concentrations of leptin, 24 patients were selected from this cohort. Although small, this subgroup proved comparable for the main outcome relevant baseline characteristics to the entire cohort, apart from age. Patients in the subgroup with serum / CSF leptin analyses were on average 5.4 years older (p = 0.018). All relevant baseline characteristics are depicted in Table 1.
Table 1
Baseline characteristics of all included patients and of patients with leptin assessment in serum and CSF.

|                          | All (n = 263) | No Leptin (n = 239) | Leptin (n = 24) | P-value* |
|--------------------------|---------------|---------------------|-----------------|----------|
| Age mean ± SD            | 53.9 ± 12.7   | 53.3 ± 12.7         | 58.7 ± 12.0     | .018     |
| Female / Male            | 192 (73.0) / 71 (27.0) | 173 (72.4) / 66 (27.6) | 19 (79.2) / 5 (20.8) | .811     |
| Hunt & Hess grade 1      | 44 (16.7)     | 43 (18.0)           | 1 (4.2)         | .185     |
| Hunt & Hess grade 2      | 61 (23.2)     | 59 (24.7)           | 3 (12.5)        |          |
| Hunt & Hess grade 3      | 83 (31.6)     | 73 (30.5)           | 10 (41.7)       |          |
| Hunt & Hess grade 4      | 45 (17.1)     | 40 (16.7)           | 5 (20.8)        |          |
| Hunt & Hess grade 5      | 30 (11.4)     | 25 (10.5)           | 5 (20.8)        |          |
| mFisher grade 1          | 63 (24.0)     | 61 (25.5)           | 2 (8.3)         | .432     |
| mFisher grade 2          | 39 (14.8)     | 35 (14.6)           | 4 (16.7)        |          |
| mFisher grade 3          | 72 (27.4)     | 67 (28.0)           | 5 (20.8)        |          |
| mFisher grade 4          | 89 (33.8)     | 75 (31.4)           | 13 (54.2)       |          |
| Aneurysm location        |               |                     |                 | .298     |
| Acom                     | 87 (33.1)     | 79 (33.0)           | 8 (33.3)        |          |
| MCA                      | 81 (30.8)     | 72 (30.1)           | 9 (37.5)        |          |
| ICA                      | 41 (15.6)     | 38 (15.9)           | 3 (12.5)        |          |
| Other                    | 54 (20.5)     | 50 (20.9)           | 4 (16.7)        |          |
| AC / PC                  | 208 (79.1) / 55 (20.9) | 191 (79.9) / 48 (20.1) | 17 (70.8) / 7 (29.2) |          |
| Aneurysm closure**       |               |                     |                 | .283     |
| clipping / endovascular  | 119 (45.2) / 141 (53.6) | 110 (46.0) / 126 (52.7) | 9 (37.5) / 15 (62.5) |          |
| Risk factors             |               |                     |                 |          |
| Smoking                  | 78 (29.7)     | 73 (30.5)           | 5 (20.8)        | .482     |
| Hypertension             | 105 (40.0)    | 93 (38.9)           | 12 (50.0)       | .189     |
| No. (%)                  | All (n = 263) | No Leptin (n = 239) | Leptin (n = 24) | P-value* |
|-------------------------|---------------|---------------------|-----------------|----------|
| DM2                     | 10 (3.8)      | 8 (3.3)             | 2 (8.3)         | .229     |
| BMI                     | 24.8 ± 5.4    | 25.7 ± 4.9          | 25.8 ± 4.3      | .855     |
| Overweight              | 90 (34.2)     | 80 (33.5)           | 10 (25.0)       | .259     |
| Obesity                 | 35 (13.3)     | 32 (13.4)           | 3 (12.5)        | .750     |
| DCI incidence           | 136 (51.7)    | 122 (51.0)          | 14 (58.3)       | .534     |
| DCI-related infarction  | 72 (27.4)     | 66 (27.6)           | 6 (25.0)        | .568     |
| DCI-related mortality   | 27 (10.3)     | 25 (10.5)           | 2 (8.3)         | .764     |
| Favorable outcome (GOSE<sub>5-8</sub>) | 162 (61.6) | 147 (61.5)          | 15 (62.5)       | .931     |

*All statistics are the results of comparing all patients without leptin measurements (n=239) versus those with leptin measurements (n = 24).

**Three patients were treated with a combination of endovascular occlusion and surgical clipping.

Acom = anterior communicating artery; AC / PC = anterior circulation / posterior circulation; BMI = body mass index; DCI = delayed cerebral ischemia; DM2 = type 2 diabetes; ICA = internal carotid artery; MCA = middle cerebral artery; mFisher = modified Fisher grade; SD = standard deviation.

**BMI, DCI and outcome**

When comparing BMI in subgroups based on DCI occurrence (noDCI = 25.2 kg/m<sup>2</sup> ± 4.4 vs. DCI = 26.0 kg/m<sup>2</sup> ± 5.1; p = 0.095), DCI-related infarction (no-infarction: 25.7 kg/m<sup>2</sup> ± 4.9 vs. infarction: 25.5 kg/m<sup>2</sup> ± 4.6; p = 0.522) and overall mortality (survivors: 25.6 kg/m<sup>2</sup> ± 4.8 vs. died: 25.7 kg/m<sup>2</sup> ± 4.9; p = 0.652) no significant differences were identified. Similarly, non-significant results were obtained when comparing patients reaching unfavorable (GOSE<sub>1-4</sub>) or favorable outcome (GOSE<sub>5-8</sub>) and between outcome groups, the mean BMI for both was almost identical (GOSE<sub>1-4</sub>: 24.8 kg/m<sup>2</sup> ± 5.6 vs. GOSE<sub>5-8</sub>: 24.9 kg/m<sup>2</sup> ± 5.2; p = 0.995) (Table 2). The incidence of DCI varied between BMI categories between 40.0–80.0%. No significant differences were noted between obesity categories regarding incidence of DCI $\chi^2$ (4, 263) = 3.969, p = 0.410; DCI-related infarction $\chi^2$ (4, 263) = 3.473, p = 0.301 or DCI-related mortality $\chi^2$ (4, 263) = 2.983; p = 0.304. Even in the extreme BMI categories, favorable outcome was reached in three out of five underweight patients and in five out of ten severely obese patients (Table 3).
Table 2
Results comparing outcome subgroups of dichotomized GOSE after 12 months. In this univariate analysis, only Hunt & Hess and mFisher, not BMI differed between outcome subgroups.

| Variables (n = 263) | Unfavorable outcome | Favorable outcome | P-value |
|---------------------|---------------------|-------------------|---------|
| GOSE                | GOSE<sub>1</sub>−<sub>4</sub> | GOSE<sub>5</sub>−<sub>8</sub> |         |
| No. (%)            | n = 101             | n = 162           |         |
| BMI, mean ± SD     | 24.8 (5.6)          | 24.9 (5.2)        | .995    |
| Dichotomized - BMI | .800                |                   |         |
| < 25 kg/m<sup>2</sup> | 53 (52.5)          | 85 (52.5)         |         |
| ≥ 25 kg/m<sup>2</sup> | 48 (47.5)           | 77 (47.5)         |         |
| Categorized - BMI  | .258                |                   |         |
| < 18.5             | 2 (2.0)             | 3 (1.9)           |         |
| ≥ 18.5; < 25       | 51 (50.5)           | 82 (50.6)         |         |
| ≥ 25; < 30         | 29 (28.7)           | 61 (37.7)         |         |
| ≥ 30; < 35         | 14 (13.9)           | 11 (6.8)          |         |
| BMI ≥ 35           | 5 (5.0)             | 5 (3.1)           |         |
| Hunt & Hess        | < .0001             |                   |         |
| Grade 1            | 5 (5.0)             | 39 (24.1)         |         |
| Grade 2            | 7 (6.9)             | 54 (33.3)         |         |
| Grade 3            | 32 (31.7)           | 51 (31.5)         |         |
| Grade 4            | 33 (32.7)           | 12 (7.4)          |         |
| Grade 5            | 24 (23.8)           | 6 (3.7)           |         |
| mFisher            | < .0001             |                   |         |
| Grade 1            | 6 (5.9)             | 57 (35.2)         |         |
| Grade 2            | 5 (5.0)             | 34 (21.0)         |         |
| Grade 3            | 38 (37.6)           | 34 (21.0)         |         |
| Grade 4            | 52 (51.5)           | 37 (22.8)         |         |
| Aneurysm closure   | .537                |                   |         |
| clipping /endovascular | 43 (42.6) / 57 (56.4)* | 76 (46.9) / 86 (53.1) |
| Unfavorable outcome | Favorable outcome |
|---------------------|------------------|

BMI = body mass index; GOSE = extended Glasgow outcome scale; mFisher = modified Fisher scale; SD = standard deviation.

*Three patients were treated with a combination of endovascular occlusion and surgical clipping.
Table 3

Results comparing clinical outcome and complications between BMI categories.

| Variables (n = 263) | Underweight | Normal weight | Overweight | Obesity - I | Obesity - II |
|---------------------|-------------|---------------|------------|-------------|-------------|
| No. (%)             | n = 263     | n = 5         | n = 133    | n = 90      | n = 25      | n = 10      | P-value     |
| DCI                 | 136 (51.7)  | 2 (40)        | 68 (51.1)  | 44 (48.9)   | 14 (56.0)   | 8 (80.0)    | .410        |
| Refractory DCI      | 65 (24.7)   | 2 (40)        | 33 (24.8)  | 18 (20.0)   | 9 (36.0)    | 3 (30.0)    | .564        |
| DCI-related infarction | 72 (27.4)  | 1 (20)        | 38 (28.6)  | 20 (22.2)   | 10 (40.0)   | 3 (30.0)    | .301        |
| Mortality           |             |               |            |             |             |             |             |
| DCI-related         | 27 (10.3)   | 1 (20)        | 14 (10.5)  | 7 (7.8)     | 5 (20.0)    | 0 (0.0)     | .304        |
| Complications       |             |               |            |             |             |             |             |
| All infections      | 102 (38.8)  | 2 (40.0)      | 52 (39.1)  | 29 (32.2)   | 12 (48.0)   | 7 (70.0)    | .200        |
| Pneumonia           | 102 (38.8)  | 2 (40.0)      | 49 (36.8)  | 33 (36.7)   | 12 (48.0)   | 7 (70.0)    | .314        |
| Sepsis              | 40 (15.2)   | 0 (0.0)       | 24 (18.0)  | 10 (7.5)    | 4 (16.0)    | 2 (20.0)    | .647        |
| UTI                 | 25 (9.5)    | 0 (0.0)       | 10 (7.5)   | 11 (12.2)   | 4 (16.0)    | 0 (0.0)     | .267        |
| ICP crises          | 66 (25.1)   | 1 (20.0)      | 28 (21.1)  | 25 (27.8)   | 8 (32.0)    | 4 (40.0)    | .667        |
| DHC                 | 52 (19.8)   | 1 (20.0)      | 24 (18.0)  | 19 (21.1)   | 4 (16.0)    | 4 (40.0)    | .197        |
| Outcome - GOSE 12 mo|             |               |            |             |             |             | .643        |
| Dead                | 55 (20.9)   | 1 (20)        | 29 (21.8)  | 15 (16.7)   | 9 (36.0)    | 1 (10.0)    |             |
| Vegetative state    | 10 (3.8)    | 1 (20)        | 4 (3.0)    | 2 (2.2)     | 2 (8.0)     | 1 (10.0)    |             |
|                   | Underweight | Normal weight | Overweight | Obesity - I | Obesity - II |
|-------------------|-------------|--------------|------------|-------------|--------------|
| Lower severe disability | 13 (4.9)    | 0 (0.0)      | 5 (3.8)    | 5 (5.6)     | 2 (8.0)      |
| Upper severe disability | 24 (9.1)    | 0 (0.0)      | 13 (9.8)   | 8 (8.9)     | 1 (4.0)      |
| Lower moderate disability | 27 (10.3) | 0 (0.0)      | 14 (10.5)  | 10 (11.1)   | 2 (8.0)      |
| Upper moderate disability | 33 (12.5)  | 1 (20)       | 12 (9.0)   | 17 (18.9)   | 2 (8.0)      |
| Lower good recovery | 43 (16.3)   | 0 (0.0)      | 22 (16.5)  | 16 (17.8)   | 2 (8.0)      |
| Upper good recovery | 58 (22.1)   | 2 (40)       | 34 (25.6)  | 17 (18.9)   | 5 (20.0)     |
| Favorable outcome | 281 (61.2)  | 3 (60.0)     | 82 (67.8)  | 60 (66.7)   | 11 (44.0)    |

|                   | Underweight | Normal weight | Overweight | Obesity - I | Obesity - II |
|-------------------|-------------|--------------|------------|-------------|--------------|
| Lower severe disability | 13 (4.9)    | 0 (0.0)      | 5 (3.8)    | 5 (5.6)     | 2 (8.0)      |
| Upper severe disability | 24 (9.1)    | 0 (0.0)      | 13 (9.8)   | 8 (8.9)     | 1 (4.0)      |
| Lower moderate disability | 27 (10.3) | 0 (0.0)      | 14 (10.5)  | 10 (11.1)   | 2 (8.0)      |
| Upper moderate disability | 33 (12.5)  | 1 (20)       | 12 (9.0)   | 17 (18.9)   | 2 (8.0)      |
| Lower good recovery | 43 (16.3)   | 0 (0.0)      | 22 (16.5)  | 16 (17.8)   | 2 (8.0)      |
| Upper good recovery | 58 (22.1)   | 2 (40)       | 34 (25.6)  | 17 (18.9)   | 5 (20.0)     |
| Favorable outcome | 281 (61.2)  | 3 (60.0)     | 82 (67.8)  | 60 (66.7)   | 11 (44.0)    |

**Early leptin levels**

There was a statistically significant positive correlation between early serum leptin levels and BMI, \(r_s(22) = 0.503; p = 0.012\) as well as early CSF leptin levels and BMI \(r_s(22) = 0.766; p < 0.001\). In a ROC analysis, early leptin concentration in serum (AUC = 0.662; 95% CI: 0.378 to 0.947, \(p = 0.258\)) and CSF (AUC = 0.712; 95% CI: 0.454 to 0.971; \(p = 0.159\)) showed no predictive value in identifying patients at risk of unfavorable outcome. Similarly, early leptin levels in serum (AUC = 0.688; 95% CI: 0.419 to 0.956; \(p = 0.137\)) and CSF (AUC = 0.571; 95% CI: 0.263 to 0.880; \(p = 0.626\)) were not associated with later DCI occurrence.

DCI = delayed cerebral ischemia; DHC = decompressive hemicraniectomy; GOSE = extended Glasgow outcome scale; ICP = intracranial pressure; UTI = urinary tract infection.
Leptin levels around DCI

Of the 14 patients who developed DCI, leptin levels in serum and CSF were compared before and during DCI occurrence. There was a non-significant increase of systemic concentrations in patients developing DCI from a median level of 5.97 ng/ml IQR to 7.22 IQR ng/ml (p = 0.410). In CSF, a statistically significant increase of leptin levels from 326.0 pg/ml IQR 171.90 to 579.2 pg/ml IQR 211.9 (p = 0.049) was observed. The comparison of both time points is depicted in Fig. 2.

Discussion

This observational study was conducted to assess whether obesity, presented by a higher BMI, is protective against DCI, and results in better clinical outcome. Our results illustrate no such association between BMI - either as a continuous or categorized variable - with DCI or clinical outcome.

The obesity paradox concerning clinical outcome in SAH emerged on the basis of oftentimes inconclusive studies. The two largest studies were based on patient registries yielding considerable case numbers but came to diverging results with one trial documenting reduced in-hospital mortality and the other rejecting the obesity paradox [6, 10]. The methodological integrity of these trials was critically addressed in a recent systematic review [27]. It remains possible that a protective effect of mild obesity exists - unspecific to SAH or stroke - potentially related to overall caloric reserves which may prove advantageous in the light of long ICU stays [18, 23]. For example, overweight defined by a body mass index between 25 and 30, is associated with lower mortality rates in patients with severe sepsis [38]. This effect was however not detected in our cohort.

A positive influence of obesity on the occurrence of DCI and hereby caused cerebral infarction has also been observed in prior research. Rinaldo et al. reported a significantly reduction of DCI in patients with higher BMI and postulated a possible neuroprotective effect of leptin [30]. These data served as incentive to substantiate the correlation of BMI and DCI with systemic and CSF levels of leptin as the possible mediator of the proposed positive effect of obesity [28]. Although a control group with healthy subjects was not available, measured leptin concentration in SAH patients transcended, in any of the evaluated time frames, the proposed normal reference range [14]. To our knowledge, there have been four previous trials assessing human leptin levels after SAH, all focusing on samples taken during the first post-hemorrhage days [11, 20, 16, 22]. All trials consistently demonstrated higher baseline leptin serum levels compared the healthy individuals. Fan et al. were the first to assess serum leptin levels in SAH patients in comparison to healthy volunteers [11]. Leptin levels proved higher in patients who suffered SAH and the height of leptin concentrations was positively correlated with the severity of disease as measured by the WFNS scale. In another observational study investigating 96 women, leptin levels remained independent of the initial clinical grade as measured by the H&H scale but gender inequalities in leptin levels may have led to bias in this investigation [16]. After SAH, serum leptin levels increase rapidly to peak after 24 hours.
Thereafter, the serum concentrations decrease gradually but remains substantially higher compared to healthy controls during the following 7 days [22]. This further illustrates the systemic nature of SAH as a disease where multiple organ systems become involved. However, leptin levels were not predictive of DCI or clinical outcome in our cohort.

Notably, DCI itself might affect the concentrations of leptin in CSF, which were significantly higher in patients after onset of DCI. As there are no indications of leptin production within the central nervous system, CSF levels are expected to be the result of transport across the blood-brain or blood-CSF barrier. Increased levels during DCI may reflect a passive accumulation of leptin mediated by injury to the blood-CSF barrier. As leptin has been proposed to also possess an immunomodulatory function, some role of leptin in the progression or internal compensatory mechanisms cannot be excluded but would certainly warrant further studies once the complex DCI cascade is better understood [3, 4, 17].

Limitations

In this cohort, the deleterious effect of underweight or severe obesity might be underestimated due to the limited number of patients included falling into these categories and caution is warranted to extrapolate our results to more extreme BMI values. Also, leptin is a hormone susceptible to diurnal variations related to feelings of hunger and satiety. These fluctuations have not been described in ICU patient and our results are based on a single daily measurement. A further limitation is the handpicked inclusion of patients in which leptin levels were assessed. As this was not performed at random, a selection bias might be present even if its character is unknown. The sample was selected to reflect the baseline characteristics of the entire cohort, but the number of patients remains fairly small increasing the chance of an error of the second kind. Finally, as with other regulators of the inflammatory response, leptin function may be modulated by local leptin concentration, the ratio between free and bound leptin, the expression of different forms of the receptors, the ratio between signaling and non-signaling receptors, and the presence of specific inhibitors [12].

Conclusion

In this analysis, obesity or increased BMI was not associated with a reduced rate of DCI and better clinical outcome. Based on these results, obesity seems not to play a relevant role in producing better or worse clinical outcome. Similarly, early leptin levels do not differ between patients developing DCI or not. After developing DCI, leptin levels in CSF increase either by active transport or disruption of the blood-CSF barrier.

Declarations

Funding -
This work was supported by the START-Program of the Faculty of Medicine, RWTH Aachen, Germany, grant number 691540.

**Conflicts of interest/Competing interests -**

There are no conflicts of interest to report.

**Availability of data and material -**

Data and material are available.

**Code availability –**

Not applicable.

**Ethics approval -**

The trial was conducted in accordance with the recommendations of the ethics committee of the Medical Faculty of the RWTH Aachen University. (EK 062/14).

**Consent to participate -**

All patients or their legal representative provided written informed consent.

**Consent for publication -**

All authors agree.

**Authors’ contributions -**

The design and conception of this trial was developed by MV, MW and WA. MV, MW, and WA were involved in data acquisition. All authors were involved in the interpretation of data. The manuscript was drafted by MV, MW and WA, and illustrations were created by MV. The final manuscript was critically revised and approved by all authors.

**References**
1. Albanna W, Weiss M, Müller M, Brockmann MA, Rieg A, Conzen C, Clusmann H, Höllig A, Schubert GA (2017) Endovascular Rescue Therapies for Refractory Vasospasm After Subarachnoid Hemorrhage: A Prospective Evaluation Study Using Multimodal, Continuous Event Neuromonitoring. Neurosurgery 80(6):942–949

2. Anzueto A, Frutos-Vivar F, Esteban A, Bensalami N, Marks D, Raymondos K, Apezteguia C, Arabi Y, Hurtado J, Gonzalez M, Tomicic V, Abroug F, Elizalde J, Cakar N, Pelosi P, Ferguson ND (2011) Influence of body mass index on outcome of the mechanically ventilated patients. Thorax 66(1):66–73

3. Baumann H, Morella KK, White DW, Dembski M, Bailon PS, Kim H, Lai CF, Tartaglia LA (1996) The full-length leptin receptor has signaling capabilities of interleukin 6-type cytokine receptors. Proc Natl Acad Sci USA 93(16):8374–8378

4. Considine RV, Sinha MK, Heiman ML, Kriauciunas A, Stephens TW, Nyce MR, Ohannesian JP, Marco CC, McKee LJ, Bauer TL et al (1996) Serum immunoreactive-leptin concentrations in normal-weight and obese humans. N Engl J Med 334(5):292–295

5. Dangayach NS, Grewal HS, De Marchis GM, Sefcik RK, Bruce R, Chhatlani A, Connolly ES, Falo MC, Agarwal S, Claassen J, Schmidt JM, Mayer SA (2018) Does the obesity paradox predict functional outcome in intracerebral hemorrhage? Journal of neurosurgery 129(5):1125–1129

6. Dasenbrock HH, Nguyen MO, Frerichs KU, Guttieres D, Gormley WB, Ali Aziz-Sultan M, Du R (2017) The impact of body habitus on outcomes after aneurysmal subarachnoid hemorrhage: a Nationwide Inpatient Sample analysis. Journal of neurosurgery 127(1):36–46

7. de Oliveira Manoel AL, Jaja BN, Germans MR, Yan H, Qian W, Kouzmina E, Marotta TR, Turkel-Parrella D, Schweizer TA, Macdonald RL (2015) The VASOGRADE: A Simple Grading Scale for Prediction of Delayed Cerebral Ischemia After Subarachnoid Hemorrhage. Stroke 46(7):1826–1831

8. de Rooij NK, Linn FH, van der Plas JA, Algra A, Rinkel GJ (2007) Incidence of subarachnoid haemorrhage: a systematic review with emphasis on region, age, gender and time trends. J Neurol Neurosurg Psychiatry 78(12):1365–1372

9. Dijkland SA, Jaja BNR, van der Jagt M, Roozenbeek B, Vergouwen MDI, Suarez JI, Torner JC, Todd MM, van den Bergh WM, Saposnik G, Zumofen DW, Cusimano MD, Mayer SA, Lo BWY, Steyerberg EW, Dippel DWJ, Schweizer TA, Macdonald RL, Lingsma HF, between-center and between-country differences in outcome after aneurysmal subarachnoid hemorrhage in the Subarachnoid Hemorrhage International Trialists (SAHIT) repository, Journal of neurosurgery (2019) 1–9

10. Elliott RS, Godoy DA, Michalek JE, Behrouz R, Elsehety MA, Hafeez S, Rios D, Seifi A (2017) The Effect of Morbid Obesity on Subarachnoid Hemorrhage Prognosis in the United States. World Neurosurg 105:732–736

11. Fan XF, Chen ZH, Huang Q, Dai WM, Jie YQ, Yu GF, Wu A, Yan XJ, Li YP (2013) Leptin as a marker for severity and prognosis of aneurysmal subarachnoid hemorrhage. Peptides 48:70–74

12. Fantuzzi G, Faggioni R (2000) Leptin in the regulation of immunity, inflammation, and hematopoiesis. J Leukoc Biol 68(4):437–446
13. Friedman JM, Halaas JL (1998) Leptin and the regulation of body weight in mammals. Nature 395(6704):763–770

14. Gijon-Conde T, Graciani A, Guallar-Castillon P, Aguilera MT, Rodriguez-Artalejo F, Banegas JR, Leptin Reference Values and Cutoffs for Identifying Cardiometabolic Abnormalities in the Spanish Population, Revista espanola de cardiologia (English ed.) 68(8) (2015) 672–9

15. Halaas JL, Gajiwala KS, Maffei M, Cohen SL, Chait BT, Rabinowitz D, Lallone RL, Burley SK, Friedman JM (1995) Weight-reducing effects of the plasma protein encoded by the obese gene. Science 269(5223):543–546

16. Huang WJ, Chen WW, Zhang X (2014) Characteristic changes in estradiol and leptin levels in patients with subarachnoid hemorrhage induced cerebral-cardiac syndrome. Eur Rev Med Pharmacol Sci 18(24):3954–3958

17. Janik JE, Curti BD, Considine RV, Rager HC, Powers GC, Alvord WG, Smith JW 2nd, Gause BL, Kopp WC (1997) Interleukin 1 alpha increases serum leptin concentrations in humans. J Clin Endocrinol Metab 82(9):3084–3086

18. Kim BJ, Lee SH, Ryu WS, Kim CK, Lee J, Yoon BW (2011) Paradoxical longevity in obese patients with intracerebral hemorrhage. Neurology 76(6):567–573

19. Kim Y, Kim CK, Jung S, Yoon BW, Lee SH (2015) Obesity-stroke paradox and initial neurological severity. J Neurol Neurosurg Psychiatry 86(7):743–747

20. Kubo Y, Koji T, Kashimura H, Otawara Y, Ogawa A, Ogasawara K (2014) Appetite loss may be induced by lower serum ghrelin and higher serum leptin concentrations in subarachnoid hemorrhage patients. Nutr Neurosci 17(5):230–233

21. Lin C, Huang SJ, Wang N, Shen ZP (2012) Relationship between plasma leptin levels and clinical outcomes of pediatric traumatic brain injury. Peptides 35(2):166–171

22. Lindgren C, Naredi S, Söderberg S, Koskinen LO, Hultin M (2016) Leptin levels after subarachnoid haemorrhage are gender dependent. SpringerPlus 5(1):667

23. Olsen TS, Dehlendorff C, Petersen HG, Andersen KK (2008) Body mass index and poststroke mortality. Neuroepidemiology 30(2):93–100

24. Platz J, Guresir E, Schuss P, Konczalla J, Seifert V, Vatter H (2013) The impact of the body mass index on outcome after subarachnoid hemorrhage: is there an obesity paradox in SAH? A retrospective analysis. Neurosurgery 73(2):201–208

25. Pobereskin LH (2001) Incidence and outcome of subarachnoid haemorrhage: a retrospective population based study. J Neurol Neurosurg Psychiatry 70(3):340–343

26. Rass V, Helbok R (2019) Early Brain Injury After Poor-Grade Subarachnoid Hemorrhage. Curr Neurol Neurosci Rep 19(10):78

27. Rautalin I, Kaprio J, Korja M, Obesity paradox in subarachnoid hemorrhage: a systematic review, Neurosurgical review (2019)
28. Rinaldo L, Rabinstein AA, Lanzino G, In Reply: Increased Body Mass Index Associated With Reduced Risk of Delayed Cerebral Ischemia and Subsequent Infarction After Aneurysmal Subarachnoid Hemorrhage, Neurosurgery (2018)

29. Rinaldo L, Rabinstein AA, Lanzino G (2019) Increased Body Mass Index Associated With Reduced Risk of Delayed Cerebral Ischemia and Subsequent Infarction After Aneurysmal Subarachnoid Hemorrhage. Neurosurgery 84(5):1035–1042

30. Rinaldo L, Rabinstein AA, Lanzino G, Increased Body Mass Index Associated With Reduced Risk of Delayed Cerebral Ischemia and Subsequent Infarction After Aneurysmal Subarachnoid Hemorrhage, Neurosurgery (2018)

31. Ryu WS, Lee SH, Kim CK, Kim BJ, Yoon BW (2011) Body mass index, initial neurological severity and long-term mortality in ischemic stroke, Cerebrovascular diseases (Basel. Switzerland) 32(2):170–176

32. Singer P, Blaser AR, Berger MM, Alhazzani W, Calder PC, Casaer MP, Hiesmayr M, Mayer K, Montejo JC, Pichard C, Preiser JC, van Zanten AR, Oczkowski H, Szczeklik S, Bischoff W (2019) S C, ESPEN guideline on clinical nutrition in the intensive care unit, Clinical nutrition (Edinburgh. Scotland) 38(1):48–79

33. Tawk RG, Grewal SS, Heckman MG, Navarro R, Ferguson JL, Starke EL, Rawal B, Hanel R, Miller D, Wharen RE, Freeman WD (2015) Influence of body mass index and age on functional outcomes in patients with subarachnoid hemorrhage. Neurosurgery 76(2):136–141

34. van Donkelaar CE, Bakker NA, Birks J, Veeger N, Metzemaekers JDM, Molyneux AJ, Groen RJM, van Dijk JMC (2019) Prediction of Outcome After Aneurysmal Subarachnoid Hemorrhage. Stroke 50(4):837–844

35. Vergouwen MD, Etminan N, Ilodigwe D, Macdonald RL (2011) Lower incidence of cerebral infarction correlates with improved functional outcome after aneurysmal subarachnoid hemorrhage. Journal of cerebral blood flow metabolism: official journal of the International Society of Cerebral Blood Flow Metabolism 31(7):1545–1553

36. Vergouwen MD, Ilodigwe D, Macdonald RL (2011) Cerebral infarction after subarachnoid hemorrhage contributes to poor outcome by vasospasm-dependent and -independent effects. Stroke 42(4):924–929

37. Vergouwen MD, Vermeulen M, van Gijn J, Rinkel GJ, Wijdicks EF, Muizelaar JP, Mendelow AD, Juvela S, Yonas H, Terbrugge KG, Macdonald RL, Diringer MN, Broderick JP, Dreier JP, Roos YB (2010) Definition of delayed cerebral ischemia after aneurysmal subarachnoid hemorrhage as an outcome event in clinical trials and observational studies: proposal of a multidisciplinary research group. Stroke 41(10):2391–2395

38. Wang S, Liu X, Chen Q, Liu C, Huang C, Fang X (2017) The role of increased body mass index in outcomes of sepsis: a systematic review and meta-analysis. BMC anesthesiology 17(1):118

39. Weir CB, Jan A, BMI Classification Percentile And Cut Off Points, StatPearls, StatPearls Publishing Copyright © 2020, StatPearls Publishing LLC., Treasure Island (FL), 2020
40. Weiss M, Conzen C, Mueller M, Wiesmann M, Clusmann H, Albanna W, Schubert GA (2019) Endovascular Rescue Treatment for Delayed Cerebral Ischemia After Subarachnoid Hemorrhage Is Safe and Effective. Front Neurol 10:136