Investigation of changes in body composition, metabolic profile and skeletal muscle functional capacity in ischemic stroke patients: the rationale and design of the Body Size in Stroke Study (BoSSS)

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Abstract

Background Stroke is steadily increasing in prevalence. Muscle tissue wasting and functional changes are frequently observed in stroke, but this has not been studied in detail yet. There is a lack of data to support guideline recommendations on how to target muscle wasting in stroke patients. We hypothesise that pathophysiological metabolic profiles and muscle functional and structural impairment are developing in stroke patients, which are associated with stroke severity and outcome after stroke.

Methods The Body Size in Stroke Study (BoSSS) is a prospective, longitudinal observation study that will explore associations between the metabolic profile, body tissue wasting and particular metabolic and functional changes in skeletal muscle tissue in stroke patients. Consecutive patients with acute stroke \((n=150)\) will be enrolled due to lacunar or territorial ischemic infarct in the area of the middle cerebral artery. Patients will be studied at annual intervals after 12 and 24 months. For comparison, healthy controls of similar age and patients with chronic heart failure will be used as control groups. The main objective is to study changes in body composition in stroke patients. Secondary, the study will focus on changes in insulin sensitivity of adipose tissue and skeletal muscle. Furthermore, measurements of endothelial function and peripheral blood flow will provide insight in the vascular regulation in stroke patients.

Conclusion This study will be the largest observational study providing insights into the metabolic and functional changes of muscle tissue in patients with acute ischemic stroke. The new data will increase our understanding of the pathophysiologic tissue wasting in stroke disease and help to develop new therapeutic strategies.

Keywords Body composition · Metabolic profile · Skeletal muscle · Wasting · Sarcopenia · Skeletal muscle functional capacity · Ischemic stroke patients

1 Introduction

In 2007, the WHO estimated an annual global average of 15 million people who will suffer from stroke leaving five
million dead and another five million disabled each year [1]. In Germany, each year, more than 262,000 people experience a new or recurrent stroke. Approximately 196,000 of these are first attacks, and 66,000 are recurrent attacks. Mortality data from 2008 indicate that stroke accounted for ≈1 of every 12 deaths in Germany [2]. On average, every 60 s, someone in Germany has a stroke. From 1998 to 2008, the stroke death rate fell by 45 %. With improved survival after stroke, the number of patients, who become disabled after stroke, is steadily increasing. More than 50 % of patients suffer motoric deficit and the costs for rehabilitation and daily support of stroke patients will rise continuously. Because of the demographical development, the numbers of stroke patients are expected to rise further.

In contrast to the intensively studied cerebrovascular dysfunctions and brain lesions in acute stroke, the systemic changes and dysregulation of peripheral organs are less well understood. Those peripheral changes include the loss and remodelling processes of skeletal muscles. There is well-accepted evidence that individuals have significantly less regional muscle mass in their paretic limbs compared with their non-paretic limbs at the chronic state after stroke [3]. However, research examining changes in whole-body muscle mass after stroke is rare. In a systematic review screening 17,042 publications, mere 14 trials were identified to specifically assess muscle changes and mechanisms of muscle loss after stroke [3]. Sample sizes in these 14 trials ranged from 6 to 83 patients with not more than 490 patients in total. These studies included both, cross-sectional and longitudinal studies, but all started 6 months post-stroke or later. Hence, information on early and mid-term post-stroke changes in the body’s ability to metabolise glucose as main energy substrate [10, 11].

The current guideline recommendations for BW management after a stroke of the European Stroke Organisation (ESO) and the USA associations (AHA/ASA) advise BW reduction [12, 13] targeting a body mass index between 18.5 and 25 kg/m² [14]. A systematic review from 2006 revealed that no prospective data are available on the effect of BW reduction on stroke in adults [15]. Moreover, a growing body of clinical data suggests a survival benefit for overweight patients after the stroke event [8, 16, 17]. More interestingly, a recent population-based study demonstrated that BW change dynamics is a stronger indicator of poor outcome after stroke than just baseline BW [18]. A recently published systematic review concluded inconsistent findings regarding changes in fat mass after stroke [19].

The complex metabolic adaptive and maladaptive processes after stroke contributing to tissue wasting and development of sarcopenia and its impact on functional capacity and stroke outcome are incompletely understood. In the current study, we aim to analyse in a prospective study whether in the long-term course of ischemic stroke disease the occurrence of metabolic dysregulation and changes in whole-body composition are paralleled by derogated patterns of muscle functional capacity and vascular regulation.

The following hypotheses will be tested:

- BW loss due to tissue wasting and change in body composition occurs in patients with ischemic stroke as a consequence of an overall catabolic/anabolic imbalance that develops in the course of the disease and includes decreased anabolic stimulation (such as from insulin resistance) and activation of catabolic hormonal systems.
- Insulin sensitivity is reduced at 1 year after an acute ischemic stroke in comparison to healthy cohorts of similar age. We hypothesise further that the degree of insulin resistance correlates with the decline in non-paretic muscle strength.
- Hormonal, metabolic and neuroendocrine patterns in stroke patients in association with changes of body composition and BW show similarities to BW loss in
other chronic diseases suggesting that stroke should be included in the complex of chronic diseases with a final common pathway of tissue wasting.

- Endothelial function is reduced by impaired regulation of endothelium-dependant vasodilatation by over-activation of the L-arginine–nitric oxide system, asymmetric dimethylarginine (ADMA) and estimating the L-arginine/ADMA ratio.

The primary objective of the study is to analyse changes in body composition (primary outcome) during follow-up after acute ischemic stroke. Changes in body composition will be measured by dual energy X-ray absorptiometry (DEXA) scanning and will be correlated to muscle function and global functional impairment. Additionally, we will analyse whether changes in body composition are accompanied by reduced insulin sensitivity, deteriorations in endothelial function and peripheral blood flow (secondary outcomes). In detail, we will investigate the insulin sensitivity of the skeletal muscle and hormonal and neurohormonal balance at whole-body level, interstitial fluid, tissue and cellular levels.

We assume that insulin resistance develops secondary to the chronic disease in stroke patients. Probably, there is a typical pathophysiologic pattern of metabolic dysregulation, neurohumoral over-activation and immune activation and that develops similar to other chronic diseases (chronic heart failure, pulmonary and renal failure) [20–22]. We want to identify common characteristics in metabolic, hormonal and immune regulatory patterns as a putative common pathway in the development of BW loss and sarcopenia in patients with stroke in comparison to other chronic diseases. The resulting data will help us to generate specific hypotheses on mechanisms underlying tissue wasting in patients after stroke.

2 Methods

2.1 Study design

The study is designed as a prospective longitudinal observation study. The study is planned as a single-centre pathophysiologic evaluation within the interdisciplinary trial programme of the Center for Stroke Research Berlin (CSB) and is funded by the German Federal Ministry of Education and Research (BMBF; grant number EO 0801). An independent external scientific advisory board approved the study design. The study has been approved by the ethics committee for all recruiting sites (EA2/008/09) and is conducted according to the Declaration of Helsinki. The study is registered at the German registry for clinical trials (Deutsches Register für Klinische Studien; DRKS) with the number DRKS00000514. The Universal Trial Number (UTN) is U1111-1116-7700.

2.2 Patient eligibility

We include patients with ischemic stroke classified as a lacunar or territorial media infarct. Consecutive patients, male and female and aged 21 years or older with ischemic stroke are screened for eligibility after admission at the emergency department of the Campus Virchow Hospital, Charité Medical University Berlin, Germany. For inclusion and exclusion criteria, see Table 1. A total of 150 patients will be enrolled according to the sample size calculation (see below). Recruitment of consecutive patients was started in June 2009 and has been finished by March 16, 2012. Twelve and 24-month follow-up recruitments are currently on going.

2.3 Planned clinical investigations and follow-up

Patients will be studied with a metabolic and functional assessment programme at baseline (Table 2). Baseline assessment will be performed during index hospitalisation after acute ischemic stroke within 5 days. For comparison of the results, we will examine two control groups of similar

| Table 1 Inclusion and exclusion criteria of the BoSSS |
|-----------------------------------------------|
| **Inclusion criteria:**                        |
| - Patient >21 years                            |
| - Patients with lacunar or territorial ischemic infarct in the area of the MCA |
| - Severity of stroke according to the National Institute of Health Stroke Scale (NIHSS) ≤12 |
| - Informed consent obtained                     |
| **Exclusion criteria:**                        |
| - Acute decompensation of causal disease necessitating intensive care therapy |
| - Chronic inflammatory disease, autoimmune disease, chronic colitis |
| - Active tuberculosis                          |
| - Organ transplantation, immunosuppressive therapy |
| - Acquired immunodeficiency syndrome           |
| - Decompensated heart failure necessitating catecholamines/inotrope substances |
| - Active myocarditis, myocardial infarction necessitating intervention |
| - COPD under oral or intravenous cortisone therapy |
| - Atrophic neuromuscular disease, liver cirrhosis, thyroid gland disease |
| - Malignancy (patients with 5 years of progression-free period can be included) |
| - Acute infections or fever, necessitating antibiotic treatment |
| - Women in fertile age without contraception and without negative pregnancy test |

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Table 2  Metabolic and functional assessment at baseline and during follow-up

| Metabolic and functional assessment at baseline | Extended metabolic and functional assessment during follow-up at 12 and 24 months |
|-----------------------------------------------|---------------------------------------------------------------------------------|
| • Neurological screening (NIHSS)               | • Baseline metabolic assessment as above                                          |
| • Functional assessment scores (mRS, Barthel index) | • Insulin resistance (i.v. glucose tolerance test)                               |
| • Body composition analysis by dual energy X-ray absorptiometry (DEXA) | • Spiroergometry                                                                 |
| • Insulin resistance by HOMA (fasting insulin and fasting glucose, C-peptide) | • Muscle biopsy                                                                  |
| • Blood and biomarker bank: metabolic/immunologic profiling | • Microdialysis of skeletal muscle and fat tissue interstitial metabolites |
| • Peripheral blood flow (venous occlusion plethysmography) | |
| • Endothelial function measured by arterial tonometry methodology (EndoPAT) | |
| • Exercise testing (isometric strength, short physical performance battery test) | |
| • Echocardiography                              | |
| • Cardiac output                                | |
| • 24 h electrocardiogram (ECG)                 | |

Metabolic and functional assessment at baseline and during follow-up

- Functional impairment that assesses performance in grading the severity of handicap and to detect changes in the Rankin scale (mRS) and Barthel index (BI) will be taken for the assessment of neurological impaired caused by stroke. The modified Stroke Scale (NIHSS) will be used to assess the severity.

At hospital admission, the National Institute of Health Stroke Program Early CT Score by an investigator blinded to the clinical/metabolic data of the patients [23].

2.4 Neurological screening and lesion imaging

At hospital admission, the National Institute of Health Stroke Scale (NIHSS) will be used to assess the severity of neurological impaired caused by stroke. The modified Rankin scale (mRS) and Barthel index (BI) will be taken for grading the severity of handicap and to detect changes in functional impairment that assesses performance in activities of daily living. Aetiology and co-morbidities will be recorded from the clinical notes. Quantitative assessment of the infarct volume will be performed using the Alberta Stroke Program Early CT Score by an investigator blinded to the clinical/metabolic data of the patients [23].

2.5 Body composition analysis

Body composition at baseline and changes over time after acute stroke will be assessed by two principal approaches that allow for detailed global and regional body composition analysis of major tissue compartments, i.e. lean tissue, fat tissue and bone tissue. DEXA scanning will be performed for the total body composition and regional distribution for trunk, appendicular and separate limb tissue mass. Body impedance assessment will be used to assess global distribution of fat tissue and fat-free mass as well as body water content and cellular integrity by phase angle and bio-impedance vector analysis [24]. Also, basic anthropometric data (body mass index, waist and hip circumference) will be assessed.

2.6 Insulin resistance

Insulin-mediated glucose uptake is pivotal for efficient energy utilisation in skeletal muscle. Particular anabolic and anti-catabolic effects are highly dependent on intact insulin sensitivity. Assessment of insulin sensitivity is therefore of central importance and the main assessment target in the evaluation of metabolic and body composition regulation. Non-diabetic subjects are planned to undergo whole-body insulin sensitivity testing using a 3-h intravenous glucose tolerance test and minimal modelling technique [25]. All metabolic studies will be performed under standardised conditions, starting in the morning, after overnight fasting and a resting period of at least 15 min in supine position in an air-conditioned quite room (metabolic day ward). After administration of a BW-adjusted glucose bolus intravenously, repeated serum samples will be obtained for profiles of glucose, insulin and C-peptide. From these profiles, individual insulin sensitivity will be assessed using the minimal modelling approach [26]. Fasting glucose, insulin profiles and HOMA [27] will be assessed as an extended measurement of insulin sensitivity.

2.7 Peripheral blood flow and cardiovascular function

Peripheral blood flow and vasodilator capacity will be assessed in the setting of stroke and the association specifically to insulin sensitivity and metabolic and hormonal regulation. Using venous occlusion (strain gauge) plethysmography, we will measure peripheral blood flow of the leg and of the forearm at rest, as post-ischemic peak blood flow and as flow-dependent flow in the non-paretic limb [28].
Quantitative determination of peripheral endothelial function will also be assessed by finger plethysmography using EndoPAT technology (Itamar Medical, Caesarea, Israel) [29]. This method has been shown to identify impaired peripheral endothelium function in stroke patients of varying aetiologies [30]. In all patients, detailed echocardiography will be recorded to assess cardiac performance (systolic, diastolic function, longitudinal and circumferential LV shortening, RV function, inter- and intraventricular asynchrony) and 24-h ECG recording (heart rate variability) will be obtained. Cardiac output will be measured by non-invasive recording using finger arterial pressure waveform analysis and measurements of systemic vascular resistance. Using the Nexfin HD device (BMEYE B.V., Amsterdam, The Netherlands), hemodynamic parameters are calculated from continuous blood pressure (in millimetre of mercury) recordings as described recently [31].

2.8 Exercise testing and muscle functional assessment

Patients, who are able to, will undergo exercise testing, in most cases, using spiroergometry. In addition to standard parameters (peak oxygen consumption, ventilatory efficiency), we will analyse further cardiorespiratory parameters, including an integrative response in ventilation, oxygen consumption and carbon dioxide production and heart rate during exercise and during recovery. Furthermore, functional performance will be tested by the Short Physical Performance Test [32]. Muscle isometric strength will be measured by the handgrip test and by the knee extension leg test assessing both the impaired and non-impaired limbs.

2.9 Serum biomarker assessment

Blood samples will be obtained in all patients under standardised conditions (see above) and will be processed and stored (−80 °C) for batch analysis of biomarkers in order to identify tools for diagnostic, prognostic and therapeutic guidance. Variables to be analysed include standard metabolic parameters, markers of neurohormonal activity (natriuretic peptides, copeptin, vasopressin, adrenomedullin, endothelin, neuro-specific enolase, protein S 100), inflammatory cytokine profiles (tumour necrosis factor (TNF)-α, interleukins such as IL-1ß, IL-6, IL-8, sphingomyelinase) and hormonal regulators of metabolic balance (insulin, adiponectin, ghrelin, leptin).

2.10 Muscle tissue metabolism

Muscle tissue metabolism will be assessed on a cellular and interstitial tissue level using biopsy analyses and microdialysis technology to obtain interstitial fluid metabolites. Tissue samples will be obtained using the Bergström needle technique from two subgroups of patients, stratified for the presence of insulin resistance. Tissue samples will be analysed using immuno-histochemical detection of inflammatory and catabolic biomarkers. Interstitial fluid metabolites will be measured in vivo using microdialysis of the skeletal muscle and subcutaneous fat tissue will be performed in patients with and without insulin resistance. Tissue interstitial fluid metabolites (glucose, pyruvate, glycerol and lactate) and inflammatory markers (TNF-α, IL-6) will be detected. To assess dynamic ranges of metabolic activity in
these tissues, microdialysis together with blood sampling will be performed in the fasted state and during an oral glucose load [33].

2.11 Neurological status, nutritional status and patient global assessment

The neurological status is determined at baseline and during follow-up by NIHSS and the physical dependency is scored by the BI and mRS tests. Several questionnaires are used for the nutritional and conditional assessment, especially the nutritional status (Mini Nutritional Assessment score) and patients’ global well-being (Subjective Global Assessment Questionnaire). Recurrence and duration of institutionalizations/re-hospitalizations and survival status will be recorded.

2.12 Sample size calculation and statistical analysis

An a priori sample size calculation has been performed based on considerations of changes in insulin sensitivity as the major pathophysiologic assessment target. It has been estimated that with 40 patients in each group (i.e. with and without insulin resistance), an assumed difference of 25 % (effect size) of the insulin sensitivity can be detected at an alpha error level of 0.05, a power of 90 % and a coefficient of variance with 29 %. This effect size is considered clinically relevant. Assuming a compliance of 55 % to attend follow-up visits after 12 and 24 months, the sample size of 150 patients at baseline was calculated. For collection of data, evaluation and statistical analysis of the initial assessments and the follow-up data, the standardized methodology will be applied as established within the CSB by research group clinical epidemiology in stroke.

Variables will be presented as mean and SD or median and IQR as appropriate. Standard statistical tests will be used for group comparison as appropriate such as unpaired and paired Student t test, analysis of variance or co-variance (ANOVA/ANCOVA) followed by Fisher's post hoc test. Distributions for biochemical variables were evaluated for normality using the Kolmogorov–Smirnov test and logarithmic transformation will be applied if necessary to allow parametric statistical approach. To analyse relationships between variables, univariable linear regression (least-squares method) and multivariable analysis will be performed. Categorical endpoints will be analysed by logistic regression. A value of $p<0.05$ is considered statistically significant. Multivariable analyses will be limited to parameters that are significant in univariable analysis. Cox proportional hazard analysis will be used to assess the association of variables with outcome variable and hazard ratios and 95 % confidence intervals will be reported.

3 Discussion

This study will be the largest prospective study with detailed assessment of changes in body composition and particularly the functional and metabolic derangements of skeletal muscle tissue after acute stroke. The discrepancies between BW management recommendations in current guidelines and emerging data may result in part from a paucity of data in patient populations and from the uncritical translation of primary prevention data to the population of patients with established disease. Clearly, there is an unmet need of observational data on whole-body composition, metabolic profile and clinical outcome in stroke patients to provide valid and specific evidence for BW management recommendations in these patients. The current study will provide insight into cellular and tissue interstitial levels of metabolites from studies in skeletal muscle tissue with microdialysis experiments and a detailed systematic set of clinical and metabolic investigations. Further, clinical data on functional status, dependency, morbidity and mortality in relation to metabolic and muscle structural changes will be accumulated in a well-characterized patient cohort. Metabolic, physical and cardiovascular functional parameters will be evaluated in cooperation between neurologists, cardiologists and endocrinologists. The combination of basic research and clinical methods of several clinical specialties underscores the true interdisciplinary approach of the study. Our findings might contribute to improve rehabilitation efforts in the early phase after stroke.

Several factors in the multifaceted interplay of metabolic regulation will be addressed in the study and should be discussed in the following. Some obvious causes such as feeding problems, immobilization and paralysis may contribute to a global negative caloric and nitrogen balance but also more complex factors such as neuroendocrine and inflammatory activation may have a role in tissue loss after stroke.

3.1 Nutritional problems and immobilization contribute to tissue wasting

Impaired feeding is well recognized as a major complication after stroke, and reduced caloric intake may well be a significant factor for negative nitrogen balance and hence tissue loss in these patients. Several studies have shown that under-nutrition is common in patients with stroke [34] and predicts outcome after stroke [4, 35]. Psycho-cognitive deficits are often observed in stroke patients, which find expression in depressive behaviour and related loss of appetite. Immobilization causes physical inactivity that may well account for disuse atrophy beyond the paralyzed limb [36, 37]. However, these factors alone may not be sufficient to explain the overall catabolic dominance resulting in muscle tissue wasting in the progression stages of stroke.
3.2 Stroke as a chronic disease promotes sarcopenia

As in other chronic diseases, such as heart failure or chronic pulmonary disease, metabolic balance is influenced by activation of the neuroendocrine and sympathetic nervous system, secretion of inflammatory cytokines and free radical stress [8, 38]. The potential role and contribution of these deleterious factors are subject to investigation in several important diseases, including but not limited to cancer, neuronal degeneration, inflammatory conditions, cardiovascular problems, diabetes mellitus and also stroke. Interestingly, all these diseases are associated with BW loss in their progression stages. Hence, a global catabolic/anabolic imbalance may develop with increased catabolic drive and unsuccessful anabolic stimulation. This would lead to tissue wasting of both fat (depletion of energy stores) and muscle tissue (functional decline) and the clinical manifestation of sarcopenia. Accordingly, a stroke-specific type of sarcopenia may be hypothesised [9].

3.3 Activation of the sympathetic and neuroendocrine systems and metabolic consequences

The sympathetic and neuroendocrine systems are likely to be involved in the metabolic imbalances after acute stroke. The acute ischemia with extended brain damage induces a global stress response in stroke patients. The acute event develops with overstimulation of the local and systemic sympathetic nervous system, hypercortisolism and activation of the hypothalamus–pituitary–adrenal axis [39, 40]. This is in line with the observation that patients with acute stroke present hyperglycemia and high glucose levels that are not correlated with HbA1c plasma levels [41, 42]. Augmented sympathetic signalling with excess of local and systemic catecholamines may account for an overall catabolic stimulation that triggers insulin resistance, protein degradation and increased lipolysis with loss of lipid energy stores. And, to close the circle, insulin resistance leads to accumulation of lipids in skeletal muscle and liver. Therefore, one of the principle objectives of the current study is to find out whether stroke patients are prone to develop insulin resistance in the course of the disease and if insulin resistance is associated with disturbed energy metabolism of the skeletal muscle. On the other hand, there is evidence that acute stroke disturbs the activity of cholinergic pathway of the vagus nerve and hence vagal reflexes. A reduction of heart rate variability (as a measure of increased neurohormonal activation tone) has been found in stroke patients and the reduced variability is associated with unfavourable functional outcomes [43, 44].

3.4 Stroke and the inflammatory cytokine network

It is well understood that inflammatory cytokines may induce tissue degradation and trigger the development of BW loss. One of the main factors responsible for muscle loss is the catabolic cytokine TNF-α [45]. Importantly, there exists a relation between stronger sympathetic tone and secretion of inflammatory cytokines. Animal models of stroke provide growing evidence that elevated catecholamine levels regulate the splenic inflammatory response to stroke through the activation of both alpha- and beta-adrenergic receptors [46]. This is concordant with a former finding that the mixed adreno-receptor blocker, carvedilol, is neuroprotective in focal cerebral ischemia and may protect the ischemic brain by inhibiting apoptosis and attenuating the expression of TNF-α and IL-1β [47].

Evidence is rising that stroke-related changes in muscle structure and function are at least in part due to local and systemic inflammation [48]. Inflammatory cytokines together with catabolic overstimulation propagate further functional decline of muscles. A recent study demonstrated that plasma concentrations of the cytokine visfatin were significantly elevated in patients with ischemic stroke [49]. Visfatin is secreted from adipocytes and stimulates upregulation of inflammatory cytokines such as TNF-α, IL-6 and IL-1β. For this reason, we seek to measure possible changes in the inflammatory cytokine network in acute and chronic stages of ischemic stroke and to investigate its relation to body composition, insulin sensitivity and patient's survival.

3.5 Summary and conclusions

Increasing evidence suggests that patients with stroke are susceptible to loss of BW (particular muscle tissue) and that this tissue wasting is a major determinant of prolonged hospitalisation and poor success of rehabilitation efforts and long-term outcome after stroke. Although some obvious causes explain tissue wasting such as feeding problems, inactivity and motor dysfunction in these patients, it is likely that more complex catabolic signalling (for example, through cytokines, oxygen-free radicals, over-stimulated sympathetic nervous system, hormonal imbalances) propagates tissue degradation and changes in body composition. Limited data are available to support BW management recommendations in patients with stroke. This study is designed to address the unmet need for long-term clinical pathophysiological studies to describe, understand and therapeutically target the complex catabolic/anabolic imbalance in patients with stroke to ultimately improve their outcome.

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Conflict of interest
There are no relevant competing interests to this manuscript.

Trial registration
The UTN is U1111-1116-7700.

Trial status
The status of this study is ongoing.

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