Body Weight After Stroke
Lessons From the Obesity Paradox

Nadja Scherbakov, MD; Ulrich Dirnagl, MD; Wolfram Doehner, MD, PhD

Background and Purpose—Outcome after acute stroke is determined to a large extent by poststroke complications. Nutritional status and metabolic balance may substantially contribute to outcome after stroke. Key mechanisms of stroke pathophysiology can induce systemic catabolic imbalance with impaired metabolic efficiency and degradation of body tissues.

Summary—Tissue wasting, sarcopenia, and cachexia may impair and delay poststroke rehabilitation and worsen the prognosis. Although current guidelines for secondary prevention after stroke recommend weight reduction, increasing evidence suggests that patients who are overweight and mildly obese may actually have a better outcome. An “obesity paradox” has been identified to describe the contrasting impact of being overweight in patients with chronic illness compared with healthy populations. We present an overview on the metabolic regulation in patients with stroke and evaluate current data on the impact of body weight and weight change after stroke. The emerging picture suggests that being overweight and obese may impact patients with stroke differently than it does healthy subjects.

Conclusions—We propose that current knowledge on obesity and its management in primary prevention cannot be transferred to patients with established stroke. Systematic studies on changes in body composition after stroke and on treatment options are warranted to establish the pathophysiology and evidence-driven management of nutritional status in these patients. (Stroke. 2011;42:3646-3650.)

Key Words: chronic disease ■ metabolic imbalance ■ obesity paradox ■ stroke ■ weight loss

See related article, page 3331.

Stroke is a leading cause of morbidity and mortality worldwide.1 The prognosis after acute stroke is serious. It is estimated that between 25% and 50% of in-hospital deaths in patients with ischemic stroke are attributed to early complications such as infections, increased intracranial pressure, nutritional status, and stroke recurrence. Weight loss after stroke appears to be a common observation.2 A multitude of mechanisms, including reduced physical activity, sympathetic activation, fever, and inflammation, may contribute to such metabolic imbalances as insulin resistance, dyslipidemia, or endothelial dysfunction. The net effect presents as an overall anabolic deficit and catabolic overactivation. As a result, accelerated tissue degradation may occur, presenting as muscle loss (ie, sarcopenia) or overall weight loss (ie, cachexia).3

We review recent findings and metabolic data from patients with stroke and pathophysiological mechanisms by which metabolic imbalance may lead to systemic wasting and poor outcome. We propose that poststroke metabolic imbalance is a clinically relevant, multifaceted, and treatable complication. We call for systematic studies on changes in body weight and composition after stroke and suggest that treating catabolic/anabolic imbalance after stroke will significantly improve long-term outcome.

Body Weight and Stroke: Before and After the Event

In the guidelines of the American Stroke Association for stroke prevention, being overweight is listed as a risk factor for stroke.4,5 The current guideline recommendations for weight management after a stroke advise weight reduction, targeting a body mass index (BMI) between 18.5 and 25 kg/m².4 These recommendations are based on a C level of evidence (ie, expert opinion) and explicitly refer to an assumed translatability of general healthy lifestyle measures known from the primary prevention setting. The beneficial effect of the weight reduction in reducing stroke risk or improving stroke outcome has never been confirmed in a clinical trial. In fact, a systematic review of reported or ongoing trials revealed that no prospective data are available on the effect of weight loss or weight reduction on stroke in adults.6 Moreover, a growing body of clinical data suggests a survival benefit for overweight patients after stroke (Table).

Thus, the Feed Or Ordinary Diet Trial collaboration, a multicenter randomized trial evaluating various feeding policies, examined a cohort of 2955 patients with stroke for 6 months and assessed nutritional status by body mass index.2 It was observed that underweight patients (BMI <20 kg/m²) had poorer survival and more complications than those with
normal weight (BMI 20–30 kg/m²) or overweight (BMI >30 kg/m²). The different outcomes between BMI sub-groups started immediately after the stroke and continued through the whole follow-up period (8 months). In a cohort of 21 884 patients from the Danish National Indicator Project registry, it was observed that poststroke mortality in the 5-year follow-up period was lower in overweight (BMI 25.0–29.9 kg/m²) and obese (BMI 30.0–34.9 kg/m²) patients than in patients with normal weight (BMI 18.5–24.9 kg/m²) and underweight (BMI <18.5 kg/m²).8

Another study examined a database of 17 648 patients with stroke, reported an age-dependent inversion of the effect of obesity on stroke outcome, and found a protective effect of overweight in elderly patients with stroke.9 In this study, stroke survivors were more likely to be overweight (BMI 25–29 kg/m²) or obese (BMI >30 kg/m²) than those without a history of stroke (64.3% versus 53.2%, P=0.003). In a prospective Greek study in 2785 patients with stroke who were followed for up to 10 years, it was observed that obesity was associated with better outcome.9 Compared with normal BMI (>25 kg/m²), obese patients (BMI ≥30 kg/m²) and overweight patients (BMI 25–29.9 kg/m²) had a 29% and 18% lower risk of 10-year mortality, respectively. Notably, the inverse association between body weight and mortality was observed as early as 1 week after stroke and continued throughout the 10-year follow-up.

In addition, not just baseline body weight, but more importantly weight change dynamics seem to be a strong indicator of poor outcome after stroke. In a recent population-based study from the Lund stroke registry with a cohort of 305 patients, weight loss of >3 kg was found in approximately one fourth of patients within both a short-term (4 months) and a medium-term (1 year) period after stroke.10 Mortality was 14% among those patients with significant weight loss and only 4% among patients without such weight loss (P<0.001).10

Controversial to these results are recent studies from the Asian region. Thus, a prospective population-based cohort study with 169 871 Chinese men and women suggested an increasing risk of stroke mortality in patients with elevated BMI.11 In addition, a study among Korean menopausal women revealed an increased risks of total stroke mortality and hemorrhagic stroke mortality with increasing BMI, particularly in those women with early menopause and those who smoked.12 These discrepancies to the former data may be due to dietary, geographic, or lifestyle differences between Asian and Western populations,11 whereas gender differences12 and of course ethnic variances may play also a role.

### The Obesity Paradox

These findings seem to be largely at variance with the recommendations for weight management for reducing cardiovascular risk and with the outlined recommendation for weight management in patients with stroke. In chronic heart failure, a bulk of data has shown that being overweight is associated with decreased mortality.13–16 In patients admitted to the emergency department due to acute, decompensated heart failure, a higher BMI was associated with lower in-hospital mortality.17 Similar findings have been reported for other chronic diseases such as chronic obstructive pulmonary disease,18 chronic kidney disease,19 rheumatoid arthritis,20 and others.

These data have recently been summarized under the term “obesity paradox.” It implies that in the setting of a chronic cardiovascular or inflammatory disease, the impact of being overweight on outcome may differ from its impact on a healthy population. From these data the presence of an obesity paradox may be concluded as well for patients after stroke. The pathophysiological explanation for the obesity paradox is, however, incompletely understood and remains a matter of ongoing discussion. Notably, most data on this topic result from observational studies and report mere associations between body composition and outcome. Those studies do not allow concluding for a direct causal interaction because indirect effects may be involved. For instance, age may be a confounder because obese patients may develop disease earlier with milder symptoms or obese patients might be treated more aggressively. These findings, clearly, point to

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the need for prospective and interventional studies to provide valid and specific evidence for weight management recommendations in patients with an established illness that may be different from the primary prevention setting.

Why Do Patients With Stroke Lose Weight?

Weight loss after stroke may be observed as the clinically overt net effect of a global negative caloric and nitrogen balance. This clinical finding may have obvious causes such as impaired feeding, inactivity, and paralysis, but metabolic balance may also be co-regulated by other factors such as neuroendocrine sympathetic activation, fever, dysregulation of appetite, cytokines, and oxygen-free radical accumulation. In the complex and interrelated web of metabolic signaling, there are a number of factors and pathways that may be abnormally activated or impaired after stroke. A global catabolic/anabolic imbalance may develop with increased catabolic drive and failing anabolic stimulation. This would lead to tissue wasting of both fat (depletion of energy stores) and muscle tissue (functional decline) and the overt clinical manifestation of weight loss. The major contributing pathways in this metabolic imbalance are discussed subsequently (see Figure 1 for an overview).

Inactivity and Reduced Intake of Calories

It is a time-honored concept that sarcopenia (ie, loss of muscle mass and lean cross-sectional area) occurs after stroke due to paresis and reduced physical activity. Physical inactivity may well account for disuse atrophy beyond the paralyzed limb. In a prospective study in 28 patients with acute stroke, a significant loss of muscle mass was detected in both the paretic (−6%) and the nonparetic leg (−5%) if patients did not regain walking capability after 2 months. Reductions in bone mineral density and increases in proportion of intramuscular fat relative to muscle area in the affected limb have also been described. The authors link these findings to immobilization. Indeed, a 10% loss of lean leg mass has been observed in healthy elderly subjects after 10 days of strict immobilization. Notably, effects of immobilization are even more pronounced in elderly hospitalized patients than in healthy subjects, because comparable lean tissue loss is already observed in hospitalized patients after only 3 days.

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 undernutrition is common in patients with stroke and predicts outcome after stroke. In fact, nutritional deficits at stroke occurrence predict subsequent continued undernutrition during poststroke hospitalization.

Clearly, inactivity is an important component of poststroke muscle atrophy, and together with impaired feeding contributes to catabolism and weight loss. On the other hand, a number of stroke-associated pathophysiological mechanisms such as stress-related neuroendocrine autonomic nervous activation, proinflammatory cytokines, increased oxygen-free radical load, and systemic hormonal imbalances may all contribute to an overall catabolic dominance. Rodent models typically demonstrate rapid and dramatic weight loss after experimental stroke, starting immediately after induction of ischemia and reaching a maximum of up to 20% within 5 days, indicating catabolic signaling beyond physical inactivity (Figure 2A–B).

Sympathetic and Neuroendocrine Activation After Stroke

Systemic neuroendocrine activation develops after stroke as a global stress response with upregulated local and systemic sympathetic activation, dysregulation in the thyroid and hypothalamus-pituitary-adrenal axis as well as decreased vagal stimulation.

Augmented sympathetic signaling may account for an overall catabolic stimulation that includes insulin resistance and increased degradation of protein and lipid energy stores. Increased lipolysis further contributes to reduced glycolytic energy use in a self-augmenting feedback cycle and results in reduced energetic efficiency and higher substrate and oxygen demands. Beside catecholamines, natriuretic peptides, particularly A-type natriuretic peptide, have also been...
shown to exert strong lipolytic signaling through a cAMP-independent pathway. Increased levels of natriuretic peptides were observed in patients after stroke parallel to stroke severity as indicated by the National Institutes of Health Stroke Scale and infarct volume.

Hypothalamic damage results in deafferentation of the vegetative system from central nervous system inhibitory sympathetic control and in dysregulation of the hypothalamic–pituitary–adrenal axis. Such dysregulation occurs at both levels, the central suppressive feedback and the stimulatory feed-forward of cortisol. As a result, cortisol and corticotropin plasma levels increase early after symptom onset and correlate to stroke severity. In addition, several studies observed hyperglycemia in patients with acute stroke, and high glucose levels that were not correlated with HbA1c plasma levels.

Mechanisms of Muscle Tissue Loss

Little is known about pathophysiological changes in skeletal muscle after stroke. Generally, paretic stroke leads to loss in muscle mass, intramuscular fat deposition, and reduction of muscle–pituitary–adrenal axis. Such dysregulation occurs at both levels, the central suppressive feedback and the stimulatory feed-forward of cortisol. As a result, cortisol and corticotropin plasma levels increase early after symptom onset and correlate to stroke severity. In addition, several studies observed hyperglycemia in patients with acute stroke, and high glucose levels that were not correlated with HbA1c plasma levels.

Conclusions

Complications during the poststroke period are major determinants of long-term outcome after stroke. Animal experiments as well as clinical evidence suggest that patients with stroke are susceptible to lose weight and that weight loss is correlated with poor outcome. Although inactivity and motor dysfunction may contribute to weight loss in these patients, it is likely that catabolic signaling (for example, through cytokines, oxygen-free radicals, or accelerated sympathetic nervous signaling) further stimulates tissue degradation and changes in body composition, which may impact on recovery and survival. No data are available to support recommendations currently made by some weight management guidelines to reduce body weight in patients after stroke. On the contrary, overweight patients appear to have a better long-term prognosis after stroke as is also the case with certain other chronic disease conditions. Experimental and long-term clinical studies are required to describe, understand, and therapeutically target the complex catabolic/anabolic imbalance in patients with stroke to ultimately improve their outcome.

Sources of Funding

The work of U.D. is supported by the Bundesministerium für Bildung und Forschung (BMBF), the German Research Foundation (ExcellenceCluster DFG-EXC 257 NeuroCure), and the European Commission’s Seventh Framework Programme (FP7/2008-2013) under grant agreements No. 201024 and No. 202213 (European Stroke Network). W.D. is supported by the Bundesministrium für Bildung und Forschung (No. 01 EO 0801), the European Commission’s Seventh Framework Programme 439 (FP7/2007-2013, grant agreement No. 241558; SICA-HF), and the Verein der Freunde und Förderer der Berliner Charité.

Disclosures

None.

References


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Table. Association Between Body Mass Index and Mortality in Patients After Stroke

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Figure 1. Schematic overview on the complex pathophysiology of systemic metabolic changes and weight loss in patients with stroke.

Figure 2. A. Mean body weight after 60 minutes of middle cerebral artery occlusion (MCAO) in the BL6 mouse strain (n=10). Note the dramatic drop and slow recovery of body weight, whereas nonmanipulated control mice gain 1 to 2 g per week. B. Correlation of infarct size with loss in body weight 72 hours after 60 minutes of MCAO. Note the very tight correlation between infarct size and loss in body weight. 95% CIs for the population mean (regression). Adapted with permission from Dimigt.10