의학박사 학위논문

Metabolic Condition and Stroke Outcome in Patients with Acute Ischemic Stroke

급성 뇌경색 환자의 대사적 상태와 뇌경색 예후에 대한 연구

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Abstract

Metabolic Condition and Stroke Outcome in Patients with Acute Ischemic Stroke

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Background and purpose: Although stroke mortality is decreasing, the socio-economic burden related to stroke is increasing due to the aging of the population. Therefore, it is very important to find modifiable factors in stroke prognosis and evaluate its impact. In this regard, metabolic conditions related to stroke are well known predictors for stroke outcomes. Among several metabolic indicators, although nutritional imbalance (malnutrition or over-nutrition) and glucose intolerance are the main elements of glucometabolic disorders, their importance is overlooked. Therefore, the effect of pre-stroke obesity status, pre-stroke glycemic control, and post-stroke nutritional support on stroke severity and functional outcome is investigated in this study.

Methods: (1) Between October 2002 and October 2019, a total of 2,826 patients from Seoul National University Hospital with AIS were recruited. To evaluate the relationship between obesity status and initial neurological severity and short-term functional outcome, obesity status was defined using body mass index (BMI). (2) A total of 1,347 patients with AIS from 2 stroke centers (Kangdong Sacred Heart

Hospital, Hallym University College of Medicine and Chuncheon Sacred Heart Hospital, Hallym University College of Medicine) from May 2016 through December 2019 were included in this analysis. To identify the association between pre-stroke glycemic control status and stroke outcome, we obtained the glycated albumin (GA) level in addition to glycated hemoglobin (HbA1c). (3) A total of 654 patients with AIS from Seoul National University Hospital were enrolled between March 2010 and May 2013. To investigate the relationship between weight change during admission and short-term functional outcome, weight change was predefined as weight gain or loss of >0.05 kg per baseline BMI unit.

Results: (1) Compared to the lowest BMI group, after adjusting for multiple covariates, the highest BMI group had a 0.3-fold risk of having moderate to severe stroke (Q5: odds ratio, 0.305; 95% confidence interval, 0.221-0.422). (2) After adjusting for multiple covariates, when compared to the lower GA group (GA<16%), the higher GA group (GA≥16%) had a 1.4-fold risk of having unfavorable short-term functional outcomes (OR 1.427; 95% CI 1.083-1.879). (3) Short-term weight loss after stroke is common than we predicted. When compared to the stable-weight group, the pronounced weight-loss group had a 2.43-fold (95% CI 1.12-5.25) risk of having unfavorable outcomes after adjusting for multiple confounders.

Conclusion: Prestroke and poststroke metabolic conditions can have a profound effect on stroke prognosis. Therefore, physicians should control the patient's modifiable metabolic risk factors to prevent stroke recurrence and sufficient nutritional supplement should be considered as an element of medical management after stroke.

Keywords: body mass index, glycated albumin, glycated hemoglobin, obesity, ischemic stroke, prognosis, metabolic disease, nutritional status

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General Introduction

Although stroke mortality has been on the decline, it remains a major cause of long-term disability and is associated with enormous socioeconomic burdens. Metabolic syndrome is a cluster of conditions including increased blood pressure,[1] hyperglycemia,[2] hyperlipidemia[3] and excess body fat.[4] A metabolic disorder occurs when the metabolic process fails and the balance is interrupted to keep the body healthy. Pre-stroke and post-stroke metabolic conditions are known to be related with outcomes after stroke. Since the prediction of the outcome after stroke may help clinicians provide effective stroke management, controlling these metabolic conditions is important. Among several metabolic parameters, although nutritional imbalance (malnutrition or over-nutrition) and glucose intolerance are the main elements of a glucometabolic disorder, their importance is overlooked. Therefore, pre-stroke obesity status, pre-stroke glycemic control, and post-stroke nutritional support were investigated.

While obesity has been an established risk factor for ischemic stroke, its effect on stroke outcome is unclear.[4] Although obesity is known to be associated with a higher risk for cerebrovascular disease, some reports have indicated that there is an inverse relationship between obesity and clinical outcomes.[5] In addition, various glycemic control parameters including initial glucose level, glycated hemoglobin (HbA1c), and glucose fluctuation have been reported to predict poor stroke outcomes but remain controversial.[6] Some parameters are not associated with cardiovascular outcome and have different prognosis depending on the period after vascular events.[7] A novel glycemic index such as glycated albumin (GA) has emerged, but its clinical implication on stroke outcome has not been established. Furthermore, patients with acute ischemic stroke (AIS) are not only prone to dehydration or malnutrition, but also at an increased risk of acquiring dysphagia. Previous articles demonstrated that post-stroke nutritional supports improve motor recovery and functional outcome.[8,9] Despite its prognostic importance, a suitable nutritional supplement after stroke did not occupy a significant part of physicians' treatment guidelines.

This study focuses on the effects of pre-stroke and post-stroke metabolic conditions on stroke outcome in AIS and aims (1) to evaluate the effect of pre-stroke obesity on the initial stroke severity and functional outcome, (2) to explore the prognostic value of GA level reflecting pre-stroke glycemic control within the recent 3 weeks as a useful predictor of short-term functional outcome, and (3) to evaluate the effects of post-stroke weight change on short-term functional outcomes.

CHAPTER 1

Pre-stroke Obesity Status is Related to Initial Stroke Severity.

Abstract

Pre-stroke Obesity Status is Related to Initial Stroke Severity.

Background and purpose: Although "obesity stroke paradox" has been documented, the exact pathomechanism is unclear. In acute ischemic stroke (AIS), initial neurological severity (INS) is generally the most significant prognostic factor, but it has not been considered in most previous reports of this paradox. Therefore, the aim of this study was to investigate the impact of obesity on INS in patients with AIS.

Methods: Between October 2002 and October 2019, a total of 2,826 patients from Seoul National University Hospital with AIS were recruited. To evaluate the relationship between obesity status and initial neurological severity and short-term functional outcome, obesity status was defined using body mass index (BMI). Multivariate binary logistic regression was conducted to investigate the associations between BMI and INS. In addition, the effect of BMI on modified Rankin Scale (mRS) 3months after stroke onset was evaluated.

Results: Among the 2,826 patients, compared to the lowest BMI group, after adjusting for multiple covariates, the highest BMI group had a 0.3-fold risk of having moderate to severe stroke (Q5: odds ratio, 0.305; 95% confidence interval, 0.221-0.422). Of the 856 patients with available 3-month mRS, patients with higher BMI levels seems to have had more favorable short-term functional outcomes. Such associations disappeared after adjusting for INS.

Conclusion: In this study, although obesity was associated with favorable functional outcomes, INS might be a more important prognostic factor. Therefore, INS should also be considered when interpreting an "obesity paradox" in chronic diseases.

Keywords: body mass index, obesity, stroke, brain ischemia, prognosis

Introduction

Obesity is known to be related to an increased number of vascular events and overall mortality.[10] However, several reports have demonstrated that obesity status was inversely correlated with clinical outcomes in patients with cardiovascular disease. This phenomenon is commonly referred to as an "obesity paradox".[11-13] This paradoxical phenomenon has been identified in variable chronic diseases such as chronic obstructive pulmonary disease, peripheral arterial disease, and chronic kidney disease.[14,15] We have previously reported that mild to moderate overweight individuals have a lower risk of long-term survival outcome after either hemorrhagic or ischemic stroke.[16,17] However, the relationship between obesity and cardiovascular outcomes showed a U- or J-shaped curve, meaning that the lowest weight group had the worst outcome. This was the unresolved issue of the obesity paradox.[18]

Since this paradoxical inverse relationship between body mass index (BMI) and stroke outcome is unclear, we focused on the effect of obesity status and initial neurological severity (INS).[5] To clarify this association in our stroke population, we extended our study population.

In this study, we investigated the effects of BMI on INS and short-term functional outcome in patients with acute ischemic stroke (AIS).

Methods

Study population

We enrolled subjects with AIS or transient ischemic attack (TIA) who were admitted within 7 days of symptom onset to Seoul National University Hospital from October 2002 through October 2019 into our prospective stroke registry system. Initially, we included a total of 3,480 patients during this period. In Analysis I, from this population, we excluded patients with incomplete medical records (n=313) and TIA (n=341). As a result, a total of 2,826 patients participated in this study. In Analysis II, we evaluated the effects of BMI on short-term outcomes by using the modified

Rankin Scale at 3 months (3-month mRS). In our registry system, the 3-month mRS was collected from March 2010; a total of 856 patients who had records concerning the 3-month mRS were included in the analysis.

All patients received standard and optimal medical therapy during hospitalization. The institutional review board of Seoul National University Hospital (1312-066-541) approved the study protocol.

Clinical information

All patients underwent diagnostic tests including routine blood tests, neuroimaging, extracranial and intracranial vascular imaging and cardiac studies. Demographic information including age and gender; stroke risk factors including hypertension (previous use of antihypertensive medication, systolic blood pressure >140 mm Hg or diastolic blood pressure >90 mm Hg at discharge), diabetes(previous use of anti-diabetic medication under the diagnosis of diabetes, HbA1c≥ 6.5%, or fasting blood glucose >7.0 mmol/L [>126 mg/dL] at discharge), dyslipidemia (previous use of lipid-lowering medication, total cholesterol >6.0 mmol/L [>240 mg/dL], or low-density lipoprotein cholesterol >4.14 mmol/L [>160 mg/dL] at admission), smoking history, and atrial fibrillation; stroke subtypes according to the Trial of Org 10172 in Acute Stroke Treatment (TOAST) classification; and laboratory data. Body weight and height were measured upon admission. BMI was calculated as the weight (kg) divided by the square of the height (m). Obesity status as a categorical variable was established by dividing BMI into five levels, according to the quintiles of BMI (Q1, <21.2; Q2, 21.2-23.0; Q3, 23.0-24.6; Q4, 24.6-26.3; and Q5, ≥26.3 kg/m^2). The lowest BMI category was used as a reference level.

Initial neurological severity (INS) was estimated using the National Institutes of Health Stroke scale (NIHSS) score upon admission. Because NIHSS scores were not normally distributed, we classified NIHSS scores into 0-7, 8-14, and ≥15. A mild stroke was defined as NIHSS 0-7, while moderate to severe stroke was

defined as NIHSS ≥8 according to the previous literature search. [19] The short-term functional outcome was estimated using the mRS at 3 months after stroke onset. The short-term functional outcome was dichotomized (favorable outcome, 3-month mRS 0-2; unfavorable outcome, 3-month mRS 3-6).

Statistical analysis

The distribution of demographic, clinical, laboratory, and stroke subtype data according to the stroke severity (mild versus moderate to severe) was analyzed using the χ^2 test, and Student's *t*-test, as appropriate. To evaluate the impact of obesity status, we did not use the predetermined guidelines for BMI such as the World Health Organization international classification recommendations or the guidelines for an Asian-Pacific population. Instead, obesity status as a categorical variable was established by dividing BMI into five levels, according to the quintiles of BMI (Q1, <21.2; Q2, 21.2-23.0; Q3, 23.0-24.6; Q4, 24.6-26.3; and Q5, ≥26.3 kg/m^2). The lowest BMI category was used as a reference level.Values for the continuous variables were expressed as the means ± standard deviation (SD). Odds ratios (ORs) and 95% confidence intervals (CIs) were expressed for the results and probability values. A probability value of ≤.05 was considered statistically significant. Analyses were performed using SPSS version 19.0 (SPSS Inc., Chicago, IL, USA).

Results

Analysis I: Body mass index and initial neurological severity

Among the 2,826 subjects, the mean age was 66±12 years, and 38.1% were women. The baseline demographic and clinical characteristics are shown in Table 1-1. A total of 2,225 patients (78.7%) were included in the mild stroke group. Compared with patients with mild stroke, patients with moderate to severe stroke (admission NIHSS≥8) were relatively older and had more frequent atrial fibrillation, and large artery atherosclerosis (LAA) and cardioembolic (CE) etiologies. In contrast, patients

with mild stroke on admission had frequent small vessel occlusion as a stroke etiology and tended to be included in the higher BMI categories.

As the obesity severity increased, while the proportion of patients with small vessel occlusion (SVO) increased (Q1, 19.7%; Q2, 23.3%; Q3, 23.7%; Q4, 27.0%; and Q5, 28.0%), the proportion of subjects with CE decreased (Q1, 28.3%; Q2, 24.1%; Q3, 22.7%; Q4, 17.2%; and Q5, 15.9%) (Table 1-2).

After categorizing all patients into the three levels of initial stroke severity (0-7, 8-14 and ≥15), obese patients were more likely to have mild stroke upon admission. Figure 1-2 shows the distribution of INS according to the BMI category. Patients with higher BMI categories had lower NIHSS scores on admission (p for trend <0.001; Figure 1-1). We adjusted for multiple covariates including age, gender, previous stroke history, hypertension, diabetes, dyslipidemia, smoking, atrial fibrillation, stroke subtypes, and BMI. When compared to the lowest BMI group, as the obesity severity increased, the risk of having moderate to severe stroke decreased (Q2, OR 0.725, 95% CI 0.549-0.958; Q3, OR 0.438, 95% CI 0.328-0.584; Q4, OR 0.347, 95% CI 0.253-0.477 and Q5, OR 0.305, 95% CI 0.221-0.422) (Table 1-3).

Table 1-1. Baseline characteristics according to the initial stroke severity

	Mild (NIHSS 0-7)	Moderate to severe (NIHSS ≥ 8)	*p*-value
No. (%)	2225 (78.7)	601 (21.3)	
Age, years	65±12	69±12	**<0.001**
Male, sex, %	1404 (63.1)	345(57.4)	**0.011**
Cardiovascular risk factor			
Prior ischemic stroke	428(19.2)	125 (20.8)	0.392
Hypertension	1415 (63.6)	389 (64.7)	0.609
Diabetes	736 (33.1)	189 (31.4)	0.450
Dyslipidemia	612 (27.5)	131 (21.8)	**0.005**
Smoking	820 (36.9)	185 (30.8)	**0.006**
Atrial fibrillation	287 (12.9)	203 (33.8)	**<0.001**
Laboratory			
White Blood Cell	7716±3094	8946±3250	**<0.001**
Hematocrit, g/dL	40.4±5.4	39.1±6.1	**<0.001**
Fasting Blood Sugar, mg/dL	110.2±38.6	119.9±42.9	**<0.001**
HbA1c, %	6.48±2.28	6.34±1.21	**0.042**
Low-density Lipoprotein, mg/dL	106.8±43.3	99.8±52.5	**0.003**
Total cholesterol, mg/dL	178.2±39.0	170.0±43.9	**<0.001**
Triglyceride, mg/dL	130.1±82.6	109.0±57.8	**<0.001**
Prothrombin Time	1.05±0.48	1.10±0.36	**0.010**
Systolic Blood Pressure, mmHg	153±28	149±28	**0.001**
Diastolic Blood Pressure, mmHg	87±16	84±16	**<0.001**
Mechanism			**<0.001**
Large artery atherosclerosis	655 (29.5)	170 (28.3)	
Small vessel occlusion	651 (29.3)	36 (6.0)	
Cardioembolic	367 (16.5)	242 (40.3)	
Undetermined	424 (19.1)	125 (20.8)	
Other determined	123 (5.5)	28 (4.7)	
BMI, Kg/m^2	24.1±3.2	22.6±3.4	**<0.001**
BMI quintiles			**<0.001**
Q1 (<21.2)	364 (16.4)	196 (32.6)	
Q2 (21.2-23.0)	389 (17.5)	141 (23.5)	
Q3 (23.0-24.6)	490 (22.0)	113 (18.8)	
Q4 (24.6-26.3)	475 (21.3)	78 (13.0)	
Q5 (≥26.3)	507 (22.8)	73 (12.1)	

Abbreviation: NIHSS= national institute of health stroke scale, BMI= body mass index, IQR= interquartile range, Q= quintiles.

No.(%) or mean±SD. *p* Values were calculated by χ^2 test for trend in proportion

Table 1-2. Associations between obesity status and stroke subtypes

	BMI Q1 (<21.2)	Q2 (21.2-23.0)	Q3 (23.0-24.6)	Q4 (24.6-26.3)	Q5 (≥26.3)	p-value
Mechanism						**<0.001**
LAA	136 (24.3)	148 (28.0)	170 (28.2)	173 (31.3)	198 (34.2)	
SVO	110 (19.7)	123 (23.3)	143 (23.7)	149 (27.0)	162 (28.0)	
Cardioembolic	158 (28.3)	127 (24.1)	137 (22.7)	95 (17.2)	92 (15.9)	
Undetermined	114 (20.4)	103 (19.5)	121 (20.1)	111 (20.1)	100 (17.3)	
Other determined	41 (7.3)	27 (5.1)	32 (5.3)	24 (4.3)	27 (4.7)	

Abbreviations: BMI= body mass index, Q= quintiles

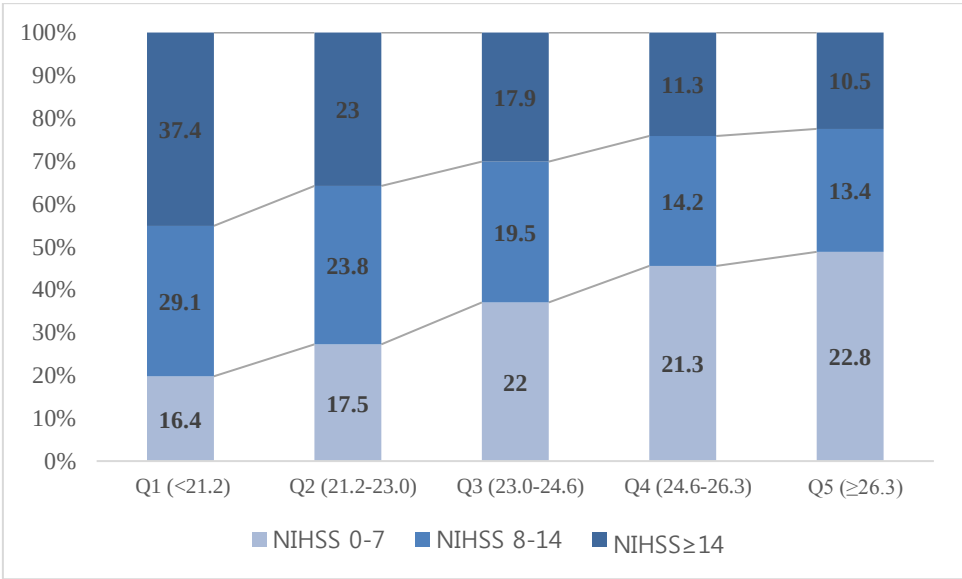

Figure 1-1. Distribution of initial neurological severities according to the levels of body mass index. ($p<0.001$)

Table 1-3. Binary logistic regression analysis for moderate to severe stroke after categorized into initial stroke severity (compared to mild stroke severity, NIHSS 0-7)

	Odds Ratio	95% Cl	*p*-value
Male, Sex	0.901	0.720-1.128	0.362
Age, per 1 years	1.013	1.004-1.022	**0.005**
Cardiovascular risk factor			
Prior ischemic stroke	1.017	0.796-1.299	0.896
Hypertension	1.231	0.986-1.536	0.067
Diabetes	1.063	0.858-1.317	0.574
Dyslipidemia	0.787	0.623-0.996	**0.046**
Smoking	0.926	0.731-1.171	0.520
Atrial fibrillation	1.613	1.198-2.171	**0.002**
Mechanism			**<0.001**
Large artery atherosclerosis	4.870	3.327-7.128	
Small vessel occlusion	reference	reference	reference
Cardioembolic	8.100	5.282-12.421	
Undetermined	4.974	3.337-7.416	
Other determined	4.410	2.548-7.633	
BMI Quintiles			**<0.001**
BMI Q5 (≥26.3)	0.305	0.221-0.422	**<0.001**
Q4 (24.6-26.3)	0.347	0.253-0.477	**<0.001**
Q3 (23.0-24.6)	0.438	0.328-0.584	**<0.001**
Q2 (21.2-23.0)	0.725	0.549-0.958	**0.024**
Q1 (<21.2)	reference	reference	reference

Abbreviation: CI= confidence interval, BMI= body mass index, Q= quintiles
Adjusted for gender, age, previous stroke history, hypertension, diabetes, dyslipidemia, smoking, atrial fibrillation, stroke subtype and body mass index.

Analysis II: Body mass index and 3-month mRS

Among a total of 856 included patients, 215 (25.1%) patients had poor functional outcomes (3-month mRS, 3-6). Patients with higher BMI categories seemed to have more favorable short-term outcomes (p for trend <0.01; Figure 1-2). In the binary logistic regression, after adjusting for age, gender, previous stroke history, hypertension, diabetes, dyslipidemia, smoking, atrial fibrillation, stroke subtype, and BMI, being overweight or obese was independently associated with better outcomes (3-month mRS, 0-2). However, after adjusting for INS, this linear association disappeared (Table 1-4).

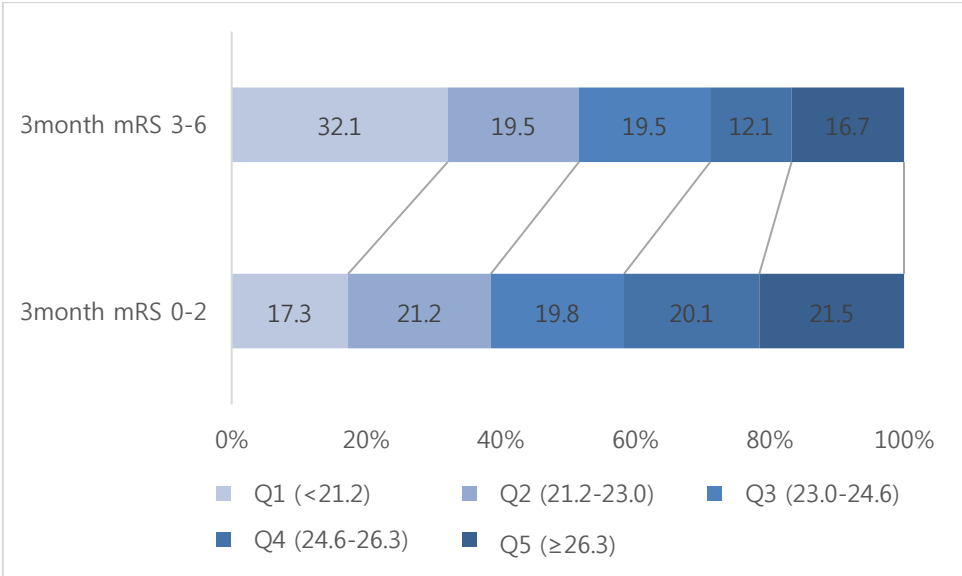

Figure 1-2. Distribution of quintiles of body mass index after dichotomizing modified Ranking scales at 3 month after stroke onset. ($p<0.001$)

Table 1-4. Binary logistic regression analysis for unfavorable outcome after categorized into 3-months mRS (compared to favorable outcome)

	Odds Ratio	95% CI	*p*-value
Model 1 BMI Q5 (≥26.3)	0.537	0.322-0.895	**0.017**
Q4(24.6-26.3)	0.372	0.215-0.645	**<0.01**
Q3(23.0-24.6)	0.539	0.331-0.878	**0.013**
Q2(21.2-23.0)	0.521	0.321-0.844	**0.008**
Q1 (<21.2)	reference	reference	reference
Model 2 BMI Q5 (≥26.3)	0.721	0.406-1.280	0.264
Q4(24.6-26.3)	0.458	0.248-0.848	**0.013**
Q3(23.0-24.6)	0.755	0.439-1.300	0.311
Q2(21.2-23.0)	0.538	0.311-0.929	**0.026**
Q1 (<21.2)	reference	reference	reference
NIHSS at admission ≥15	13.133	7.173-24.046	**<0.001**
8-14	10.373	6.200-17.353	**<0.001**
0-7	reference	reference	reference

Abbreviations: CI = confidence interval, BMI= body mass index, Q= quintiles
Model 1: Adjusted for gender, age, previous stroke history, hypertension, diabetes, dyslipidemia, smoking, atrial fibrillation, stroke subtype and body mass index.
Model 2: model 1 plus initial neurological severity

Discussion

The main findings of this study are as follows; (1) patients in a higher BMI category had a milder stroke at admission than those in a lower BMI category, and (2) patients in a higher BMI category had a favorable short-term functional outcome at 3 months after stroke onset; however, in a model adjusted for INS, this significance disappeared. Therefore, we suggest that INS is a more potent predictor for stroke outcome than obesity.

Several previous studies have supported an "obesity paradox". Vemmos et al. found that in 2,785 Greek patients with stroke, who were followed for up to 10 years, obesity was associated with better outcomes.[20] In a database of 17,648 patients with stroke, obesity was associated with lower mortality in elderly overweight and obese patients.[21] Obese patients might have more metabolic reserves in catabolic states, such as heart failure, chronic kidney disease, and stroke.[21] However, because the clinical stroke outcome is determined by complex conditions including concomitant comorbidities, we assessed it from different perspectives. As reported previously, we suggest that obese patients may have less severe strokes initially and may therefore have better functional outcomes.[5]

In this study, patients with higher BMI categories presented initially with mild stroke severity. We cannot explain the exact pathomechanism about these phenomena. We may assume that obese patients may more often take preventive cardiovascular drugs and be under health control because of their conventional risk factors. According to a prior report, a higher BMI category is associated with an increased use of guideline-recommended medical treatment such as antiplatelet, renin-angiotensin system inhibitor and lipid-lowering drugs.[22] Another notable point is that socioeconomic status may affect patients' attention to health. In contrast to developed countries, in developing countries, those with a higher educational status or a higher social status tend to be obese.[23] In Korea, the association between BMI and socioeconomic status becomes largely mixed for men and mainly negative for women.[24] Therefore, Korean people with a higher socioeconomic status tend to be

overweight or mildly obese.

Interestingly, it is noteworthy that obese patients had stroke subtype of small vessel occlusion, whereas lean patients had a stroke subtype of cardioembolism (Table 1-4). The relationship between obesity and stroke classification has not yet been firmly studied.[25] Our results propose that elevated BMI levels may yield an unknown mechanism for provoking the development of small-vessel disease. In the Hisayama study, increased BMI was a risk factor for lacunar infarction in a Japanese population.[25] In addition, adipose tissue seems to produce a tissue necrosis factor receptor.[26] Furthermore, when compared to CE stroke, lacunar infarction showed significantly lower plasma levels of tumor necrosis factor-α, interleukin-6, and interleukin-1β.[27] Although we cannot explain the causal relationship between BMI and small vessel occlusion etiology, a significant association was noted between BMI and stroke subtypes sharing inflammatory patho-mechanisms.

The strength of this study is that it focuses on reviewing the "obesity-stroke paradox" in terms of INS. Prior studies supporting the "obesity paradox" have evaluated the relation between obesity and mortality or outcomes. Despite this novel finding, there are some caveats to this study. First, because this is a retrospective observational study, unknown confounding factors might affect our results. Second, we did not include any information on pre-stroke medication history. Third, BMI is not a direct measurement of body composition, such as body fat composition, waist-hip ratio or abdominal circumference. Finally, the mean BMI is relatively low compared to the WHO international classification. However, BMI distribution depends on ethnicity, and it would be better to use BMI quintiles to investigate the correlation between BMI and stroke severity or outcomes.

In conclusion, we suggest that the "obesity-stroke paradox" was not clear, at least in ischemic stroke patients. However, it should be noted that this study addresses some critical issues. Further prospective studies are warranted to confirm these issues, and it is premature to generalize the "obesity paradox".

CHAPTER 2

Pre-stroke Glycated Albumin is Associated with Short-Term Functional Outcome After Acute Ischemic Stroke.

Abstract

Pre-stroke Glycated Albumin is Associated with Short-Term Functional Outcome After Acute Ischemic Stroke.

Background and purpose: Glycated albumin (GA) reflect the short-term control of glycemic status over the recent 2 to 4 weeks and could be a useful marker not influenced by situations that alter glycated hemoglobin (HbA1c) levels. There is growing interest to use a new biomarker such as GA, but data are limited linking this indicator to outcomes in acute ischemic stroke (AIS). In addition, the role of GA for predicting stroke outcome in AIS has not been assessed previously. Therefore, the aim of this study was to explore the prognostic value of GA as a useful predictor for short-term functional outcome compared to HbA1c.

Methods: Patients with AIS from 2 stroke centers (Kangdong Sacred Heart Hospital, Hallym University College of Medicine and Chuncheon Sacred Heart Hospital, Hallym University College of Medicine) from May 2016 through December 2019 were enrolled. Among a total of 1,405 patients, 58 subjects who were not evaluate for GA levels were excluded. As a result, a total of 1,347 patients were included in this analysis. To identify the association between pre-stroke glycemic control status and stroke outcome, patients were divided into two groups according to the GA levels (GA<16% versus GA≥16%). The short-term functional outcome was estimated using the modified Rankin Scale (mRS) at 3 months after stroke onset.

Results: Among the 1,347 patients, 595 patients (44.2%) were included in the GA≥16% group. After adjusting for multiple covariates, when compared to the lower

GA group (GA<16%), the higher GA group (GA≥16%) had a 1.4-fold risk of having unfavorable short-term functional outcomes (OR 1.427; 95% CI 1.083-1.879). However, HbA1c was not significantly associated with short-term outcomes at 3 month after stroke onset.

Conclusion: GA level is associated with short-term functional outcome after AIS and might be a better prognostic biomarker than HbA1c. Although the impact of GA on stroke outcome is undervalued in the current stroke guidelines, monitoring GA in addition to HbA1c could improve the glycemic control in subjects with AIS.

Keywords: glycated albumin, glycated hemoglobin, brain ischemia, stroke, prognosis, biomarkers, blood glucose

Introduction

Glycated hemoglobin (HbA1c) reflects glycemic control over the past 2-to 3-month period and has been the gold standard for the management of diabetes. Nonetheless, HbA1c has some clinical limitations; it does not reflect recent glycemic status, and a number of conditions (eg, anemia, erythropoietin treatment, transfusion, and kidney disease) affect the test result.[28] Therefore, there is growing interest to use new biomarkers such as fructosamine or glycated albumin (GA), but data are limited linking this indicator to outcomes in ischemic stroke. GA reflects exposure to glycemic control approximately over the recent 2 to 4 weeks, reflecting the turnover of plasma proteins. Therefore, GA reflects the short-term control of glycemic status compared with HbA1c and could be a useful marker not influenced by situations that alter HbA1c levels. Additionally, because it is measured by a standardized enzymatic methodology, it is easy and fast to perform.[29] Multiple parameters including initial glucose level, HbA1c, and glucose fluctuation have been reported to predict poor stroke outcomes but remain controversial.[29] In this regard, there have been some needs for detecting a novel index for diagnosing and managing glycemic control in covering the short-term effect in many critical illnesses. Furthermore, the role of GA for predicting stroke outcome in AIS has not been assessed previously.

Therefore, in this chapter, we aimed to explore the prognostic value of GA as a useful predictor for short-term functional outcome compared to HbA1c.

Methods

Study population

We enrolled patients with acute ischemic stroke (AIS) or transient ischemic attack (TIA) who were admitted within 7 days of symptom onset to two stroke centers (Kangdong Sacred Heart Hospital, Hallym University College of Medicine and Chuncheon Sacred Heart Hospital, Hallym University College of Medicine) from May 2016 through December 2019 into our prospective stroke registry system.

Among a total of 1,405 patients (541 patients from Kangdong Sacred Heart Hospital and 864 patients from Chuncheon Sacred Heart Hospital), fifty-eight subjects who were not evaluate for GA levels were excluded. As a result, a total of 1,347 patients were included in this analysis (Figure 2-1).

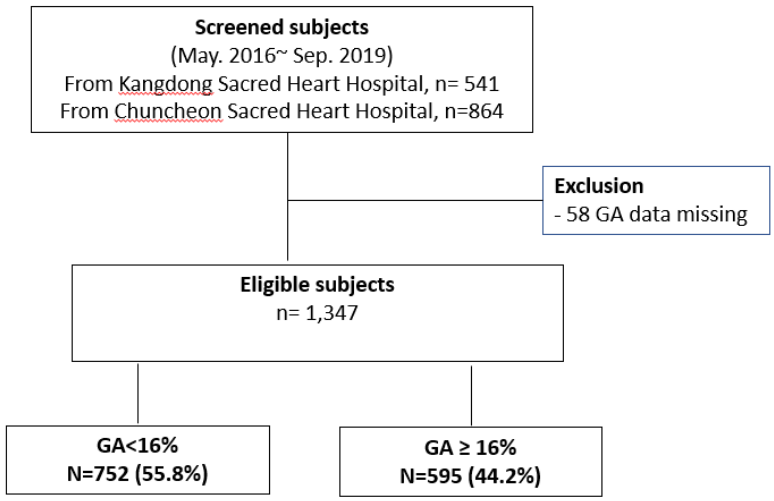

Figure 2-1. Flow diagram of study population

All patients received standard and optimal medical therapy during hospitalization. The institutional review board of the three centers (Kangdong Sacred Heart Hospital IRB no. 2020-02-006-001 and Chuncheon Sacred Heart Hospital IRB no. 2017-89) approved the study protocol, and written informed consent was obtained from all participants or from the next of kin when the patient's agreement was not possible.

Clinical information

All patients underwent diagnostic tests including routine blood tests, neuroimaging, extracranial and intracranial vascular imaging and cardiac studies. Demographic information including age and gender; stroke risk factors including hypertension (previous use of antihypertensive medication, systolic blood pressure >140 mm Hg or diastolic blood pressure >90 mm Hg at discharge),

diabetes(previous use of anti-diabetic medication under the diagnosis of diabetes, HbA1c≥ 6.5%, fasting blood glucose >7.0 mmol/L [>126 mg/dL] at discharge), dyslipidemia (previous use of lipid-lowering medication, total cholesterol >6.0 mmol/L [>240 mg/dL], or low-density lipoprotein cholesterol >4.14 mmol/L [>160 mg/dL] at admission), smoking history, and atrial fibrillation; stroke subtypes according to the Trial of Org 10172 in Acute Stroke Treatment (TOAST) classification; and laboratory data. Body weight and height were measured upon admission. Body mass index (BMI) was calculated as the weight (kg) divided by the square of the height (m). Obesity status as a categorical variable was established by dividing the BMI into four levels, according to the BMI quartiles (Q1, <21.57; Q2, 21.57-23.78; Q3, 23.78-25.97; and Q4, ≥25.97 kg/m^2). The lowest BMI category was used as a reference level. GA levels were measured by an enzymatic method using albumin-specific proteinase and ketoamine oxidase (Beckman Coulter AU5821 Biochemical Analyzer; Tokyo, Japan). Since the reference interval for GA is different from the studies, we divided the population into two groups (GA<16% versus GA≥16%).

Initial neurological severity (INS) was estimated using the National Institute of Health Stroke scale (NIHSS) score on admission. The short-term functional outcome was estimated using the modified Rankin scale (mRS) at 3 months after stroke onset. The short-term functional outcome was dichotomized (favorable outcome, 3-month mRS 0-2; unfavorable outcome, 3-month mRS 3-6).

Statistical analysis

The distribution of demographic, clinical, laboratory, and stroke subtype data according to the GA levels (GA<16% versus GA≥16%) was analyzed using the χ^2 test and Student's *t*-test, as appropriate. The trend in baseline data was also calculated using the χ^2 test for trends in proportion. In Analysis I, the associations between the BMI and the GA levels were estimated using χ^2 test analyses. In Analysis II, we evaluated the associations between GA levels and functional

outcomes at 3 months after stroke onset.

Values for the continuous variables were expressed as the means ± standard deviation (SD). Odds ratios (ORs) and 95% confidence intervals (CIs) were expressed for the results and probability values. A probability value of ≤.05 was considered statistically significant. Analyses were performed using SPSS version 19.0 (SPSS Inc., Chicago, IL, USA).

Results

Analysis I: Levels of glycated albumin and short-term functional outcome

Among the 1,347 subjects, the mean age was 69.6±13.0 years, and 59.8% were men. The baseline demographic and clinical characteristics are shown in Table 2-1. A total of 595 patients (44.2%) were included in the GA≥16% group. Patients with GA≥16% were older and had some prevalent conventional vascular risk factors, such as prior ischemic stroke, hypertension, diabetes, smoking history, and atrial fibrillation. Whereas patients with GA≥16% did not have severe initial stroke severity, and shot-term unfavorable functional outcome (3 month mRS, 3-6) was prevalent (25.7% versus 38.6%) (Table 2-1 and Figure 2-2).

Table 2-1. Baseline characteristics according to levels of glycated albumin

	Glycated Albumin<16%	Glycated Albumin≥16%	*p*-value
No. (%)	752 (55.8)	595 (44.2)	
Age, years	67±13	72±12	**<0.001**
Male, sex, %	470 (62.5)	336 (56.5)	**0.025**
BMI at admission, kg/m^2	23.99±3.33	23.84±3.74	0.424
Cardiovascular risk factor			
Prior ischemic stroke	131 (17.4)	156 (26.2)	**<0.001**
Hypertension	425 (56.5)	411 (69.1)	**<0.001**
Diabetes	102 (13.6)	363 (61.0)	**<0.001**
Dyslipidemia	104 (13.8)	97 (16.4)	0.197
Smoking	184 (24.5)	97 (16.3)	**<0.001**
Atrial fibrillation	106 (14.1)	120 (20.2)	**0.009**
Antiplatelet history	177 (23.5)	180 (30.3)	**0.010**
Anticoagulation history	29 (3.9)	38 (6.4)	**0.042**
Mechanism			**<0.001**
LAA	247 (33.2)	233 (39.5)	
SVO	225 (30.2)	119 (20.2)	
Cardioembolic	116 (15.6)	109 (18.5)	
Other determined	35 (4.7)	21 (3.6)	
Undetermined	121 (16.3)	108 (18.3)	
Laboratory			
White Blood Cell	7743±2626	7805±2848	0.677
Hemoglobin, g/dL	14.0±1.8	13.4±2.10	**<0.001**
Platelet	233K±67K	224K±71K	**0.017**
FBS, mg/dL	117.2±34.0	159.5±72.4	**<0.001**
Initial glucose, mg/dL	124.1±35.4	170.5±74.3	**<0.001**
HbA1c, %	5.59±0.58	6.99±1.57	**<0.001**
HbA1c≥6.5%	42 (5.6)	321 (54.2)	**<0.001**
Glycated albumin, %	13.8±1.3	20.1±4.8	**<0.001**
GA/HbA1c	2.47±0.32	2.89±0.49	**<0.001**
Initial glucose/GA	8.94±2.63	8.32±3.03	**<0.001**
Initial glucose/HbA1c	22.01±6.38	23.80±8.11	**<0.001**
LDL, mg/dL	103.3±33.6	100.4±36.5	0.129
Total cholesterol, mg/dL	171.5±43.2	163.9±44.2	**0.002**
Triglyceride, mg/dL	136.3±101.0	133.5±78.9	0.590
Blood urea nitrate	16.9±10.5	19.3±10.0	**<0.001**
Creatinine	0.94±0.61	1.01±0.86	**0.002**
Albumin,	3.98±0.42	3.93±0.47	**0.043**
Prothrombin Time	1.07±0.47	1.08±0.21	0.726
hsCRP	7.67±23.33	13.85±34.34	**<0.001**
Systolic BP, mmHg	151±28	148±28	0.090
Diastolic BP, mmHg	86±15	84±15	**0.023**
Initial Stroke Severity, NIHSS 0-7	585 (77.8)	481 (80.8)	0.172
NIHSS ≥8	167 (22.2)	114 (19.2)	
Poor short-term functional outcome, (3 month mRS, 3-6)	181 (25.7)	214 (38.6)	**<0.001**

Abbreviation: BMI, Body mass index; FBS, Fasting blood sugar; GA, Glycated albumin; LDL, Low density lipoprotein; HDL, High density lipoprotein; aPTT, activated prothrombin time; LAA, Large artery atherosclerosis; SVO, Small vessel occlusion; hsCRP, high sensivity C-reactive protein; BP, Blood pressure; IQR, Interquatile ratio; NIHSS, National Institutes of Health Stroke Scale

No. (%) or mean±SD. *p* Values were calculated by $\chi 2$ test for trend in proportion

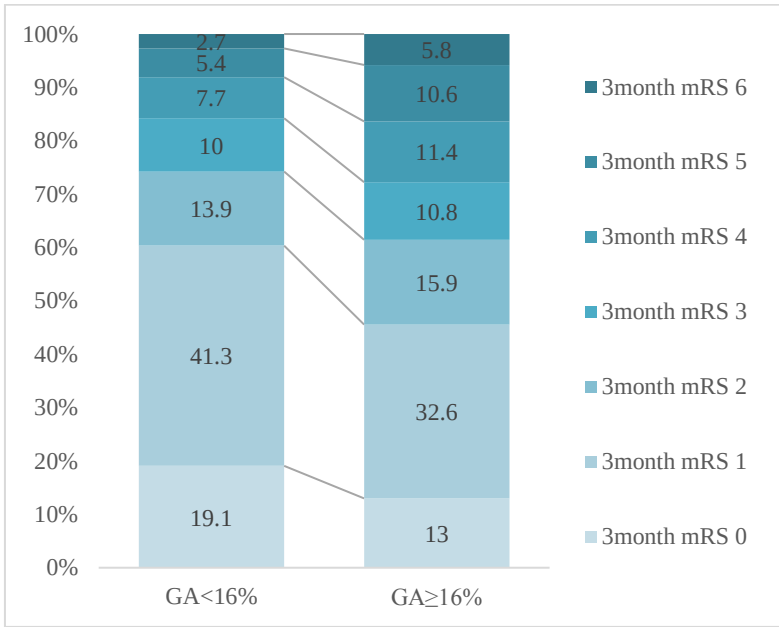

Figure 2-2. Distribution of levels of glycated albumin after dichotomizing modified Rankin scale (mRS) at three-months after stroke onset.

Table 2-2. Baseline characteristics according to short-term functional outcomes

	Good functional outcome 3 month mRS, 0-2	Poor functional outcome 3 month mRS, 3-6	*p*-value
No. (%)	863 (68.6)	395 (31.4)	
Age, years	67±13	75±12	**<0.001**
Male, sex, %	552 (64.0)	197 (49.9)	**<0.001**
BMI at admission, kg/m^2	24.08±3.35	23.54±3.88	**0.011**
BMI Quartile 1	196 (23.0)	113 (29.0)	**0.009***
2	205 (24.0)	100 (25.6)	
3	228 (26.7)	91 (23.3)	
4	224 (26.3)	86 (22.1)	
Cardiovascular risk factor			
Prior ischemic stroke	155 (18.0)	114 (28.9)	**<0.001**
Hypertension	507 (58.7)	263 (66.6)	**0.008**
Diabetes	279 (32.3)	154 (39.0)	**0.021**
Dyslipidemia	112 (13.0)	62 (15.7)	0.195
Smoking	202 (23.4)	50 (12.7)	**<0.001**
Atrial fibrillation	96 (11.1)	107 (27.1)	**<0.001**
Antiplatelet history	213 (24.7)	123 (31.1)	**0.046**
Anticoagulation history	21 (2.4)	38 (9.6)	**<0.001**
Mechanism			**<0.001**
LAA	304 (35.6)	148 (37.6)	
SVO	268 (31.4)	63 (16.0)	
Cardoembolic	111 (13.0)	94 (23.9)	
Other determined	35 (4.1)	16 (4.1)	
Undetermined	136 (15.9)	73 (18.5)	
Laboratory			
White Blood Cell	7657±2532	7992±3153	0.064
Hemoglobin, g/dL	13.9±1.9	13.2±2.2	**<0.001**
Platelet	230K±64K	228K±79K	0.615
FBS, mg/dL	134.0±58.8	139.8±58.2	0.099
Initial glucose, mg/dL	144.0±61.3	146.1±60.7	0.562
HbA1c, %	6.19±1.31	6.26±1.39	0.453
HbA1c≥6.5%	236 (27.4)	111(28.3)	0.731
Glycated albumin, %	16.2±4.5	17.3±4.6	**<0.001**
Glycated albumin ≥16%	341 (39.5)	214 (54.2)	**<0.001**
GA/HbA1c	2.61±0.40	2.75±0.52	**<0.001**
Initial glucose/GA	8.89±2.53	8.54±2.75	**0.027**
Initial glucose/HbA1c	22.96±6.58	23.28±7.03	0.437
LDL, mg/dL	102.8±35.0	100.5±36.1	0.280
Total cholesterol, mg/dL	169.4±43.1	164.8±45.2	0.084
Triglyceride, mg/dL	142.1±93.2	121.8±93.3	**0.001**
Blood urea nitrate	17.1±9.2	19.7±11.3	**<0.001**
Creatinine	0.97±0.69	1.08±0.88	**0.037**
Albumin,	4.01±0.39	3.84±0.51	**<0.001**
Prothrombin Time	1.07±0.45	1.09±0.18	0.482
hsCRP	7.54±23.92	16.66±37.20	**<0.001**
Systolic BP, mmHg	149±27	150±29	0.630
Diastolic BP, mmHg	85±15	84±16	0.153
Initial Stroke Severity, NIHSS 0-7	724 (83.9)	274 (69.4)	**<0.001**
NIHSS ≥8	139 (16.1)	121 (30.6)	

Abbreviation: BMI, Body mass index; FBS, Fasting blood sugar; GA, Glycated albumin; LDL, Low density lipoprotein; HDL, High density lipoprotein; aPTT, activated prothrombin time; LAA, Large artery atherosclerosis; SVO, Small vessel occlusion; hsCRP, high sensivity C-reactive protein; BP, Blood pressure; IQR, Interquatile ratio; NIHSS, National Institutes of Health Stroke Scale. No. (%) or mean±SD. *p* Values were calculated by $\chi 2$ test for trend in proportion

Table 2-3. Correlations between body mass index and Glycemic control indicators

	BMI, Q1	BMI, Q2	BMI, Q3	BMI, Q4	*p*-value
No. (%)	331 (24.6)	328 (24.4)	339 (25.2)	333 (24.7)	
Age, years	72±14	71±13	68±12	67±13	**<0.001**
Male, sex, %	174 (52.6)	190 (57.9)	235 (69.3)	198 (59.5)	**<0.001**
BMI at admission, kg/m^2	19.76±1.68	22.71±0.63	24.79±0.64	28.35±2.62	**<0.001**
Cardiovascular risk factor					
Prior ischemic stroke	78 (23.6)	69 (21.0)	73 (21.5)	63 (18.9)	0.539
Hypertension	179 (54.1)	197 (60.1)	218 (64.3)	228 (68.5)	**<0.001***
Diabetes	97 (29.3)	112 (34.1)	121 (35.7)	131 (39.3)	**0.007***
Dyslipidemia	36 (10.9)	47 (14.3)	53 (15.7)	63 (18.9)	**0.004***
Smoking	60 (18.1)	65 (19.8)	80 (23.7)	74 (22.2)	0.299
Atrial fibrillation	71 (21.5)	48 (14.6)	43 (12.7)	60 (18.0)	**0.043**
Mechanism					**0.028**
LAA	112 (34.1)	118 (36.5)	138 (40.8)	107 (32.5)	
SVO	68 (20.7)	90 (27.9)	94 (27.8)	89 (27.1)	
Cardoembolic	65 (19.8)	49 (15.2)	48 (14.2)	57 (17.3)	
Other determined	23 (7.0)	10 (3.1)	9 (2.7)	14 (4.3)	
Undetermined	60 (18.3)	56 (17.3)	49 (14.5)	62 (18.8)	
Laboratory					
White Blood Cell	7687±2776	7753±2719	7882±2793	7789±2618	0.773
Hemoglobin, g/dL	13.0±2.2	13.5±2.0	14.1±1.8	14.1±1.8	**<0.001**
Hematocrit, g/dL	39.1±7.4	40.2±5.4	41.6±5.1	42.6±16.6	**<0.001**
Platelet	231K±76K	233K±77K	227K±59K	224K±63K	0.735
FBS, mg/dL	130.3±53.6	139.4±66.7	132.4±50.5	140.6±58.1	0.053
Initial glucose, mg/dL	139.1±56.0	145.5±65.3	143.2±56.3	150.5±62.0	0.126
HbA1c, g/dL	5.99±1.19	6.25±1.39	6.25±1.34	6.35±1.36	**0.003**
HbA1c≥6.5%	70 (21.3)	85 (26.0)	95 (28.1)	111(33.4)	**<0.001***
Glycoalbumin, %	16.8±4.6	16.8±4.7	16.2±4.3	16.4±4.7	0.294
Glycoalbumin Quartiles					**0.001***
Glycoalbumin, 1Q	58 (17.5)	68 (20.7)	104 (30.7)	98 (29.4)	
Glycoalbumin, 2Q	80 (24.2)	91 (27.7)	75 (22.1)	85 (25.5)	
Glycoalbumin, 3Q	109 (32.9)	81 (24.7)	79 (23.3)	65 (19.5)	
Glycoalbumin, 4Q	84 (25.4)	88 (26.8)	81 (23.9)	85 (25.5)	
GA/HbA1c	2.77±0.51	2.69±0.48	2.58±0.39	2.57±0.41	**<0.001**
LDL, mg/dL	96.0±32.5	100.8±34.8	105.8±35.6	104.7±36.0	**0.001**
Total cholesterol, mg/dL	162.0±41.7	168.8±46.5	171.0±43.1	170.7±43.5	**0.023**
Triglyceride,mg/dL	106.8±53.7	130.3±81.8	149.7±120.7	153.9±93.9	**<0.001**
Blood urea nitrate	19.5±12.1	17.6±10.9	17.1±8.1	17.5±10.1	**0.024**
Creatinine	1.07±0.98	0.98±0.83	0.94±0.45	1.00±0.59	0.135
Albumin,	3.85±0.49	3.95±0.46	4.03±0.41	4.01±0.38	**<0.001**
Prothrombin Time	1.13±0.69	1.05±0.11	1.07±0.24	1.06±0.14	**0.035**
hsCRP	13.87±39.0	9.15±22.7	9.77±28.5	9.04±23.1	0.143
Systolic BP, mmHg	147±28	151±28	151±29	150±27	0.379
Diastolic BP, mmHg	83±13	84±15	86±16	87±16	**0.013**
3-month mRS, 0-2	196 (63.4)	205 (67.2)	228 (71.5)	224 (72.3)	**0.009***

Abbreviation: BMI, Body mass index; FBS, Fasting blood sugar; LDL, Low density lipoprotein; HDL, High density lipoprotein;
aPTT, activated prothrombin time; LAA, Large artery atherosclerosis; SVO, Small vessel occlusion; BP, Blood pressure; IQR, Interquatile ratio; NIHSS, National Institutes of Health Stroke Scale

No. (%) or mean±SD. *p* Values were calculated by $\chi 2$ test for trend in proportion
*Linear by linear association for trend.

After categorizing all patients into the two groups according to short-term functional outcome (favorable, 3-month mRS= 0-2, versus unfavorable, 3-month mRS= 3-6), patients with unfavorable short-term outcome were older, less obese, and more likely to have conventional vascular risk factors including prior ischemic stroke, hypertension, diabetes, and atrial fibrillation (Table 2-2). While HbA1c was not significantly different between two groups (6.19±1.31 versus 6.26±1.39), GA level was significantly higher in subjects with unfavorable outcome (16.2±4.5 versus 17.3±4.6). Figure 2-2 shows the distribution of short-term functional outcomes (3-month mRS) according to the GA levels.

As the severity of obesity increased, age was decreased (BMI Q1, 72±14; Q2, 71±13; Q3, 68±12; and Q4, 67±13). As the obesity severity increased, while the proportion of patients with HbA1c≥6.5% increased (Q1, 21.3%; Q2, 26.0%; Q3, 28.1%; and Q4, 33.4%), the proportion of subjects with higher GA level showed decreasing trends (Table 2-3).

We adjusted for age, sex, BMI, prior ischemic stroke history, hypertension, diabetes, smoking, atrial fibrillation, TOAST classification, hemoglobin, triglyceride, blood urea nitrogen, high sensitivity C-reactive protein (hsCRP), initial stroke severity and GA (Table 2-4). After adjusting for multiple covariates, when compared to the lower GA group (GA<16%), the higher GA group (GA≥16%) had a 1.4-fold risk of having unfavorable short-term functional outcome (OR 1.427; 95% CI 1.083-1.879). Increased age, prior ischemic stroke, atrial fibrillation, TOAST classification and initial stroke severity (NIHSS≥8) are statistically significant predictors of unfavorable short-term outcome. A higher BMI exhibited a significant relationship with short-term favorable functional outcome in univariate analysis, but the significance disappeared in multivariate analysis.

Table 2-4. Effect of GA on unfavorable short-term outcomes (compared to favorable 3-month mRS 0-2)

Variables	OR	95% CI	*P*-value
Age, per 1 years	**1.036**	**1.022-1.050**	**<0.001**
Male, sex	0.743	0.548-1.007	0.056
BMI at admission, kg/m^2	1.000	0.961-1.041	0.982
Cardiovascular risk factor			
Prior ischemic stroke	**1.679**	**1.223-2.306**	**0.001**
Hypertension	0.860	0.636-1.164	0.329
smoking	0.917	0.613-1.370	0.671
Atrial fibrillation	**1.891**	**1.109-3.225**	**0.019**
Mechanism			
LAA	**1.686**	**1.166-2.437**	**0.005**
SVO	reference		
Cardioembolic	1.459	0.795-2.678	0.223
Other determined	1.797	0.828-3.899	0.138
Undetermined	1.469	0.937-2.303	0.094
Hemoglobin	0.980	0.906-1.059	0.609
Triglyceride	0.999	0.998-1.001	0.415
Blood urea nitrogen	1.009	0.995-1.022	0.198
hsCRP	**1.007**	**1.002-1.012**	**0.005**
Initial Stroke Severity, NIHSS 0-7	reference		
NIHSS ≥8	**1.914**	**1.383-2.648**	**<0.001**
Glycated albumin <16%	Reference		
Glycated albumin ≥16%	**1.427**	**1.083-1.879**	**0.012**

Adjusted for age, sex, body mass index, prior ischemic stroke, hypertension, smoking, atrial fibrillation, stroke subtype, hemoglobin, triglyceride, blood urea nitrogen, hsCRP, initial stroke severity, and glycated albumin.

Abbreviation: BMI, Body mass index; hsCRP, high sensitivity C-reactive protein; mRS, modified Rankin Scale; OR, Odds Ratios; CI, confidence intervals; NIHSS, National Institutes of Health Stroke Scale

In addition, analyses of the effects of several glycemic control parameters on short-term functional outcomes are shown in Table 2-5. When GA was replaced by other glycemic control parameters in the same model, continuous levels of GA, GA≥16%, and GA/A1c ratio were significantly associated with unfavorable stroke outcomes at 3 months (3-month mRS 3-6), while continuous levels of HbA1c and HbA1c≥6.5 failed to show significant association.

Table 2-5. Effect of Glycemic control parameters on unfavorable short-term outcomes (compared to favorable 3-month mRS 0-2)

Variables	OR	95% CI	*P*-value
HbA1c	1.082	0.977-1.199	0.130
HbA1c≥6.5%	1.176	0.866-1.596	0.300
GA/HbA1c	**1.409**	**1.025-1.937**	**0.035**
Glycated albumin	**1.037**	**1.007-1.067**	**0.014**
Glycated albumin ≥16%	**1.427**	**1.083-1.879**	**0.012**

Adjusted for age, sex, hypertension, diabetes, dyslipidemia, smoking, atrial fibrillation, stroke subtype, glycated albumin and body mass index.

Abbreviation: GA, Glycated albumin; OR, Odds Ratios; CI, confidence intervals

To reduce the influence of people whose function was not good before the stroke, 48 subjects with pre-mRS 4 or 5 were excluded. Among a total of 1,299 patients, multivariate binary logistic regression was conducted. After adjusting for multiple covariates, when compared to the lower GA group (GA<16%), the higher GA group (GA≥16%) had a 1.4-fold risk of having unfavorable short-term functional outcome (OR 1.425; 95% CI 1.074-1.892) (Table 2-6).

Table 2-6. Effect of GA on unfavorable short-term outcomes (compared to favorable 3-month mRS 0-2) (after excluding patients with pre-mRS 4-5)

Variables	OR	95% CI	*P*-value
Age, per 1 years	**1.032**	**1.018-1.047**	**<0.001**
Male, sex	0.802	0.586-1.098	0.169
BMI at admission, kg/m^2	1.008	0.968-1.050	0.707
Cardiovascular risk factor			
Prior ischemic stroke	**1.497**	**1.073-2.089**	**0.018**
Hypertension	0.838	0.616-1.140	0.261
smoking	0.948	0.634-1.417	0.794
Atrial fibrillation	**2.106**	**1.229-3.608**	**0.007**
Mechanism			
LAA	**1.589**	**1.090-2.316**	**0.016**
SVO	reference		
Cardioembolic	1.331	0.718-2.469	0.364
Other determined	1.596	0.716-3.559	0.253
Undetermined	1.409	0.891-2.227	0.142
Hemoglobin	0.974	0.898-1.057	0.531
Triglyceride	0.999	0.997-1.001	0.247
Blood urea nitrogen	1.007	0.993-1.021	0.310
hsCRP	**1.007**	**1.002-1.012**	**0.009**
Initial Stroke Severity, NIHSS 0-7	reference		
NIHSS ≥8	**1.881**	**1.349-2.622**	**<0.001**
Glycated albumin <16%	Reference		
Glycated albumin ≥16%	**1.425**	**1.074-1.892**	**0.014**

Adjusted for age, sex, body mass index, prior ischemic stroke, hypertension, smoking, atrial fibrillation, stroke subtype, hemoglobin, triglyceride, blood urea nitrogen, hsCRP, initial stroke severity, and glycated albumin.

Abbreviation: BMI, Body mass index; hsCRP, high sensitivity C-reactive protein; mRS, modified Rankin Scale; OR, Odds Ratios; CI, confidence intervals; NIHSS, National Institutes of Health Stroke Scale

Analysis II: Levels of glycoalbumin and short-term functional outcome by glucose tolerance status

To investigate the relationship between GA and short-term functional outcome by glucose tolerance status, patients were classified into two groups based on diabetes history. In the binary logistic regression, after adjusting for multiple covariates, GA≥16% was independently associated with unfavorable short-term outcome only in patients without diabetes (Table 2-7).

Table 2-7. Effect of GA on unfavorable short-term outcomes (compared to favorable 3-month mRS 0-2) based on the presence of diabetes

	Patients with diabetes			*Patients without diabetes*		
Variables	OR	95% CI	*P*-value	OR	95% CI	*P*-value
Age, per 1 years	**1.037**	**1.012-1.062**	**0.004**	**1.036**	**1.019-1.054**	**<0.001**
Male, sex	0.824	0.496-1.368	0.454	**0.669**	**0.452-0.992**	**0.046**
BMI at admission, kg/m^2	0.999	0.930-1.073	0.982	0.996	0.947-1.048	0.881
Cardiovascular risk factor						
Prior ischemic stroke	**1.792**	**1.087-2.956**	**0.022**	**1.608**	**1.053-2.456**	**0.028**
Hypertension	0.877	0.502-1.535	0.647	0.853	0.589-1.236	0.400
Smoking	0.890	0.454-1.744	0.734	0.942	0.563-1.576	0.819
Atrial fibrillation	0.567	0.212-1.518	0.259	**3.194**	**1.590-6.417**	**0.001**
Mechanism						
LAA	**2.319**	**1.230-4.370**	**0.009**	1.446	0.910-2.296	0.118
SVO	reference			reference		
Cardoembolic	7.268	**2.312-22.852**	**0.001**	0.699	0.320-1.528	0.369
Other determined	3.511	0.717-17.192	0.121	1.547	0.620-3.860	0.349
Undetermined	**2.743**	**1.256-5.989**	**0.011**	1.043	0.592-1.839	0.883
Hemoglobin	0.932	0.822-1.057	0.274	1.053	0.944-1.175	0.353
Triglyceride	0.999	0.996-1.002	0.553	0.999	0.997-1.002	0.597
Blood urea nitrogen	1.010	0.986-1.034	0.436	1.005	0.988-1.023	0.555
hsCRP	1.006	0.998-1.014	0.149	**1.008**	**1.002-1.014**	**0.008**
Initial Stroke Severity, NIHSS 0-7	Reference			Reference		
NIHSS ≥8	1.563	0.879-2.779	0.129	**2.102**	**1.401-3.153**	**<0.001**
Glycoalbumin <16%	Reference			Reference		
Glycoalbumin ≥16%	0.847	0.492-1.459	0.551	**1.778**	**1.212-2.607**	**0.003**

Adjusted for age, sex, hypertension, diabetes, dyslipidemia, smoking, atrial fibrillation, stroke subtype, glycated albumin and body mass index.

Abbreviation: BMI, Body mass index; LAA, large artery atherosclerosis; SVO, small vessel occlusion; mRS, modified Rankin Scale; OR, Odds Ratios; CI, confidence intervals

Discussion

The main findings of this study were as follows; (1) patients with a higher GA level (GA≥16%) had unfavorable short-term functional outcomes at 3 month after stroke onset; (2) a higher GA and higher GA/A1c ratio was significantly associated with unfavorable short-term functional outcome at 3 month after stroke onset, but HbA1c was not; and (3) a higher GA level was associated with unfavorable short-term functional outcome at 3 months after stroke onset only in patients without diabetes.

Several studies demonstrated that GA was associated with vascular calcification and mortality.[28,30] In the Atherosclerosis Risk in Communities (ARIC) study of 11,104 participants, elevated baseline GA was significantly associated with cardiovascular outcomes even after adjustment for traditional risk factors, with especially strong associations in patients with DM.[28] In a 49 hemodialysis subjects with type 2 DM, GA was significantly associated with the presence of peripheral vascular calcification and seems to be a better indicator of glycemic control than HbA1c.[30] However, few studies have evaluated the role of GA in IS patients.[6,31] In a subanalysis of the CHANCE (Clopidogrel in High-Risk Patients with Acute Nondisabling Cerebrovascular Events) trial, GA could be a potential marker to predict the effects of dual and single antiplatelet therapy on recurrent stroke.[31] In a total of 296 AIS patients with DM, higher GA (≥16%) was significantly associated with a severe stroke (NIHSS>14) and large infarct volume.[6] Nevertheless, the relationship between GA and stroke outcome has not been assessed previously. In the present study, higher GA (≥16%) could increase the risk of unfavorable short-term functional outcome after stroke. One explanation for this finding is that higher GA increases infarct volume.[6] According to previous reports, GA may be a good marker of macrovascular complication, while HbA1c is a good marker of microvascular complication.[6] In this regard, it is partially explained that LAA etiology accounts for a larger proportion in the group with higher GA in this study.

Interestingly, we found that when GA was replaced by HbA1c (both continuous levels or HbA1c ≥6.5%) in the same model, HbA1c failed to prove the significant association. Similar to our study, some previous articles reported that HbA1c was not an independent predictor of short-term outcomes.[32,33] In a retrospective study of 317 diabetic patients with acute coronary syndrome, HbA1c levels before admission are not related to short-term cardiovascular outcome including in-hospital mortality, 6-month major adverse cardiovascular events (MACE), and all-cause mortality.[32] In an observational multicenter study of 608 patients with acute myocardial infarction, HbA1c was not associated with 7-day

mortality and 30-day mortality.[33] However, the results are still controversial. Some authors demonstrated that HbA1c was a potential indicator for in-hospital death in patients with acute coronary syndrome[7] and was a good predictor of acute and long-term mortality in patients with AIS.[34] Furthermore, in a total of 534 subjects with AIS treated with mechanical thrombectomy, HbA1c≥6.5% was an independent predictor of a poor outcome at 3 months after AIS.[2] We cannot explain the exact pathomechanism, compared to HbA1c, GA is known to more accurately reflect short-term glucose fluctuation.[35]

Interestingly, we found that the effect of GA on short-term stroke outcome would differ according to concomitant DM. After classifying by DM, effect of GA on functional outcome at 3-month was significant only in patients without DM (OR 1.670, 95% CI 1.170-2.386). Consistent with our result, among all 2,496 participants with AIS (2,077 non-diabetic versus 419 diabetic), elevated admission glucose level is associated with increased risk for 30-day case fatality in patients without DM.[36] According to Huh et al, fasting glucose and postprandial glucose could influence GA/A1c ratio in the prediabetes and type 2 DM groups, while those variables did not influence GA/A1c ratio in the normal glucose tolerance group. [37] This result suggests that the influence of glycemic control parameters may be different according to glucose tolerance status. We hypothesized that in patients with previously identified DM, gluco-insulin homeostasis, drug interaction, and insulin resistance may also affect the result. This finding is meaningful because this suggests that since the DM state itself is an adverse factor, GA or GA/A1c cannot be an appropriate index without considering glycemic control status. Further well-designed study to investigate the relationship between glycemic control indicators and glucose tolerance status should be needed.

In addition, the effect of BMI on GA might also be considered to evaluate the role of GA on stroke outcome. According to previous reports, in spite of the inconsistent results, obesity seems to be negatively associated with GA or GA/A1c.[37-40] In this study, the BMI showed a significantly positive correlation with

HbA1c, while BMI negatively correlated with GA or GA/A1c (Table 2-3). At present, the reasons for the negative influence of BMI on GA are not clear. However, possible explanation is as follows: (1) Salas-Salvado et al. demonstrated that albumin levels are lower in obese subjects than non-obese counterparts.[41] But Miyashita et al. found that obese children had higher albumin concentration than non-obese children,[42] and Koga et al. reported no correlation between BMI and albumin levels.[38] (2) turnover of albumin may be increased in obese patients. Since chronic low-grade systemic inflammation is involved in obese subjects, inflammation might increase the catabolic rate of albumin and decrease the rate of albumin synthesis. The authors did not provide the exact mechanism, but hypothesized that inflammation represented by elevated hs-CRP was significantly associated with BMI, which could result in lower GA.[38] In our study, when BMI is increasing, while GA showed a decreasing trend, albumin showed an increasing trend. Therefore, we suggest that it affects albumin turnover rather than the albumin concentration itself.

The major strength is that this is the first study to evaluate the effect of GA on short-term functional outcome in patients with AIS. Second, this is a multicenter study with a relatively large sample size. In this regard, GA is expected to be a new glucose control marker in patients with AIS. However, several limitations should be noted in our study. First, this was a cross sectional observational study design. Second, although we controlled for some confounders in this statistical model, some confounding factors may affect the result. Third, we did not evaluate all conditions of affecting protein metabolism such as thyroid dysfunction, liver cirrhosis, and nephrotic syndrome. Fourth, we could not present changes of blood sugar tests during admission or infarct growth at symptom aggravation. Therefore, we cannot provide direct evidence that GA, an indicator reflecting glucose fluctuation, is related to worse functional outcome. Finally, although we considered the effect of glucose tolerance status by DM status, we did not adjust for insulin resistance status because of the lack of serum insulin level.

In conclusion, we suggest that GA level is associated with short-term functional outcome after AIS and might be a better prognostic biomarker than HbA1c. Although the role of GA on stroke outcome is undervalued in the current treatment guidelines, monitoring GA in addition to HbA1c could improve the glycemic control in patients with AIS.

CHAPTER 3

Post-stroke Weight Change is Related to Short-Term Functional Outcome After Acute Ischemic Stroke.

Abstract

Post-stroke Weight Change is Related to Short-Term Functional Outcome After Acute Ischemic Stroke.

Background and purpose: Because the intentional weight loss is associated with a reduced risk for the development of obesity-related metabolic diseases, it is generally recommended that those who are obese should lose excessive weight. However, benefit of weight loss among patients with a recent acute ischemic stroke (AIS) is unclear. Although controversy exists regarding weight modifications, little is known about the impact of weight loss on stroke prognosis. Therefore, the purpose of this study was to evaluate the prognostic importance of weight change for the short-term functional outcomes in patients with AIS.

Methods: A total of 654 patients with AIS from Seoul National University Hospital were enrolled between March 2010 and May 2013. Weight change of each participant between admission and discharge was assessed. Weight change was defined as change ≥0.05 kg/baseline body mass index (BMI)-unit. The short-term functional outcome were evaluated using a modified Rankin Scale (mRS) at three-months after the onset of a stroke. To investigate the relationship between weight change during admission and short-term functional outcome, the "calorie surplus" was calculated to define the groups of weight change during the stroke period.

Results: Among the 654 subjects, the weight change group was 35.2% (n=230). Weight loss occurred in 24.6% of the participants during the hospitalization following the stroke, which lasted an average of 9 days. When compared to the stable-weight group, the pronounced weight-loss group had a 2.43-fold (95% CI

1.12-5.25) risk of having unfavorable outcomes after adjusting for multiple confounders.

Conclusion: Short-term weight loss after stroke appears to be more common than we expected and is associated with unfavorable short-term functional outcomes. Therefore, sufficient nutritional supplement should be considered as an element of medical management after stroke.

Keywords: stroke, brain ischemia, prognosis, nutritional status

Introduction

Obesity is a well-known risk factor for the development of cardiovascular disease and death.[10,43,44] It is generally recommended that those who are obese should lose excessive weight.[45] Weight reduction in subjects with metabolic syndrome is recommended because it helps reduce plasma renin activity and improve glucose intolerance.[46,47] Conventionally, the intentional weight loss was associated with a reduced risk for the development of obesity-related metabolic disorders.[48,49] However, recent guidelines proposed that despite the beneficial effects of weight loss on cardiovascular risk, benefit of weight loss among patients with a recent TIA or ischemic stroke is unclear.[50]

In addition, several studies have indicated a puzzling phenomenon (obesity paradox), in which overweight and obese subjects have favorable outcomes compared with normal or under-weight individuals.[15,16,20] In this regard, although obese patients might have more metabolic reserves in catabolic states, little is known about the impact of weight loss on stroke prognosis.[20]

Although controversy exists regarding weight modifications, several researches have reported that weight gain or weight fluctuation was associated with a significantly higher mortality risk than the maintenance of a stable weight. [51, 52] In contrast, some reports have demonstrated that weight loss may be associated with a higher mortality.[45, 47, 51, 53, 54] It is a point of note that weight loss after stroke is a common phenomenon, and no less than a quarter of patients who were healthy before the onset of a stroke experienced weight loss.[55, 56] Therefore, the aim of this study was to evaluate the prognostic importance of weight change for the short-term functional outcomes in patients with AIS.

Methods

Study population

We enrolled patients with AIS or TIA who were admitted within 7 days of the onset

of symptoms to our stroke center from March 2010 through May 2013 into our prospective stroke registry system. A total of 732 patients were recruited at Seoul National University Hospital. All participants were followed through telephone interviews or medical records via the outpatient department. From this population, we excluded patients with errors in their medical records (n=13), lack of data regarding weight at discharge (n=7), and follow-up loss (n=28). In addition, patients with a duration of the hospitalization over 30 days (n=30) were also excluded. Since the aim of this study was to evaluate the impact of weight change during AIS on short-term functional outcomes, we think that a very long hospitalization might affect the interpretation of the result. As a result, a total of 654 subjects were included in this study (Figure 3-1).

All patients received standard, optimal medical treatment during their hospitalization. The institutional review board of Seoul National University Hospital (1408-049-600) approved the study protocol, and written informed consent was obtained from all participants or from the next of kin when the patient's agreement was not possible.

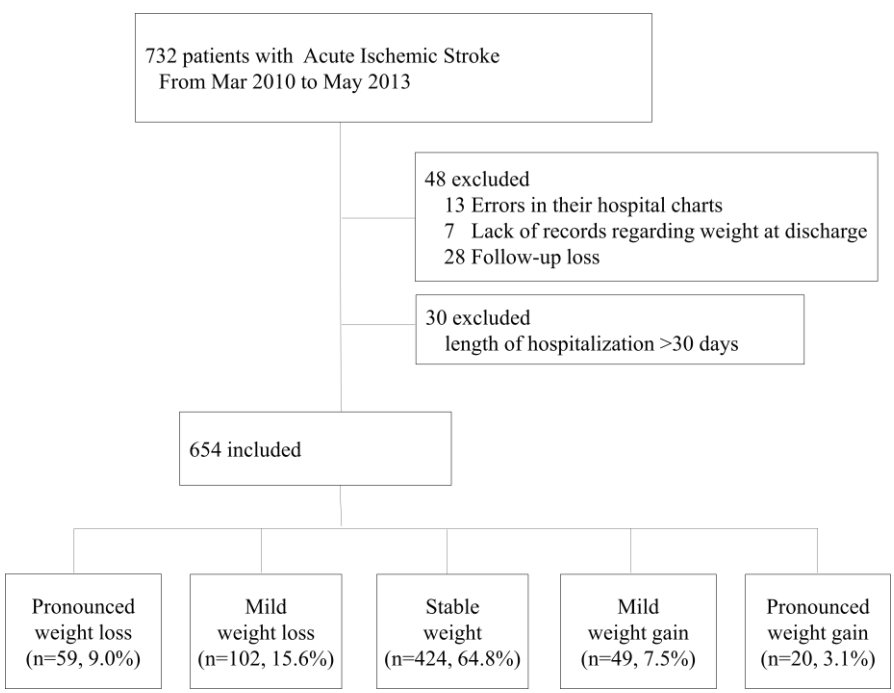

Figure 3-1. Flow diagram of study population

Clinical information

All patients underwent routine blood tests, brain imaging, extracranial and intracranial vascular imaging, and cardiac work-ups. We evaluated demographic information including age, and gender; stroke risk factors including hypertension, diabetes, smoking history, previous stroke history, and atrial fibrillation; stroke subtypes according to the Trial of Org 10172 in Acute Stroke Treatment (TOAST) classification; and laboratory data. We measured the body weight and height at admission and then the body weight again at discharge. In cases that were referred to other departments, we obtained the weight at the time of discharge from the department of Neurology. Body weight was measured using a calibrated automatic height and weight scale (model GL-150, G-Tech International, Uijeongbu-si, Gyeonggi-do, South Korea) by a trained nurse, with hospital gown and shoes off. In cases of severe stroke, we obtained the body weight using an under-bed scale, and the height was measured using a tapeline. The body mass index (BMI) was calculated as the weight (kg) divided by the square of the height (m). For the BMI categories, we used the suggestions for an Asian-Pacific population. Weight change was predefined as weight gain or weight loss of >0.05 kg per baseline BMI unit, as described in a prior study. [54] We thought that this definition was more reasonable for evaluating weight change than other methods that have been used, defining weight change as a gain or loss of more than 1-2 kg/m^2, a gain or loss of 4-5% of the body weight or a gain or loss of more than 3 kg.[45, 47, 48, 51, 52, 57] Consequently, for a patient with a BMI of 30 kg/m^2, a change of >±1.5 kg was classified as a weight change. Patients were categorized into 5 groups with regard to weight change: those with pronounced weight gain or loss (>0.1 kg/baseline BMI-unit), those with mild weight gain or loss (≥0.05-0.1 kg/baseline BMI-unit), and those with a stable weight (<0.05 kg/baseline BMI-unit).

We evaluated the kilocalorie consumption at 3 days after stroke onset based on the physician's diet prescriptions. Because some patients might be on a fasting status during the initial 1-2 days due to initial neurological deterioration or operability

considerations. When patients had dysphagia at the time of admission, we provided sufficient calories through the Levin tube, as needed. We defined a "calorie surplus" as follows: calorie surplus = kilocalorie intake (Kcal) at 3 days after stroke onset – basal metabolic expenditure (BME).[58] The BME was calculated by the Harris-Benedict equation set up in 1918.

Men: BME (Kcal) = 66 + (13.7) (weight, Kg) + (5) (height, cm) – (6.8) (age, years)

Women: BME (Kcal) = 655 + (9.6) (weight, Kg) + (1.7) (height, cm) – (4.7) (age, years)

The Harris-Benedict equation is a method used to estimate an individual's BME and kilocalorie necessities per day. The resulting range is the recommend daily kilocalorie consumption to keep the current body weight. [58, 59] The type of meals served at 3 days were divided into three categories: general diet, tube feeding, and fasting.

The INS was estimated using the NIHSS score on admission. Because NIHSS scores were not normally distributed, we categorized NIHSS scores into three groups (0-7, 8-14, and ≥15).[19] The short-term functional outcome was estimated using the mRS at 3 months after stroke onset. The 3-month mRS was obtained via an outpatient visit or structured telephone interview. We evaluated the distribution of the weight changes after dichotomizing the mRS at 3 months after stroke onset (favorable outcome = 3-month mRS 0-2 versus unfavorable outcome = 3-month mRS 3-6). [60]

As an obligatory social insurance, the Korean medical insurance (National Health Insurance) covers the whole population living in the country. Therefore, "health insurance" covers approximately 96-97% of the Korean population and "Medicaid" for the poor, covers the remaining 3-4% of the population, with an annual evaluation of the poverty status.

Statistical analysis

The distributions of demographic records, clinical features, laboratory findings, hospital period, and stroke etiology data according to the weight change were analyzed using the χ^2 test, Student's *t*-test, or one-way analysis of variance (ANOVA), as appropriate. The trend in the baseline data was also calculated using the χ^2 test for trends in proportion. In the binary logistic regression analysis, we conducted the associations between weight change and the short-term functional outcomes. The stable weight (<0.05 kg/baseline BMI-unit) was used as a reference. For the dependent variables, patients with a favorable outcome (3-month mRS 0-2) were used as a reference group in the binary logistic regression analysis.

The values for the continuous variables were expressed as the means ± standard deviation (SD). The odds ratios (ORs) and 95% confidence intervals (CIs) are presented in the results and were used to calculate the probability values. A probability value of ≤.05 was considered statistically significant. Analyses were performed using SPSS version 21.0 (SPSS Inc., Chicago, Ill., USA).

Results

Of the 654 patients, the mean age was 67±13 years, and 61.5% of the participants were men. The mean duration of hospitalization was 9.4±5.2 days. The baseline demographic and clinical characteristics are shown in Table 3-1. The weight change group was 35.2% (n=230). Approximately a quarter of patients (24.6%) was included in the weight loss group (Figure 3-2). Patients with pronounced weight loss had higher initial BMI, smaller calorie surplus at 3 days after stroke onset, more likely to have fasting or feeding diet, and atrial fibrillation. In contrast, patients with stable weight had the mildest neurological severity on admission and the shortest length of hospital stay (Table 3-1). Among a total of the 654 subjects, more than a quarter of patients (26.1 %) had poor functional outcomes. Figure 3-3 shows the distribution of the short-term functional outcomes (3-month mRS) according to the weight change levels. Patients with weight loss had unfavorable functional outcomes compared to those with stable weight (*p* for difference <0.001; Figure 3-3).

Table 3-1. Baseline characteristics grouped by weight change

	Pronounced weight loss	Mild Weight loss	Stable	Mild Weight gain	Pronounced weight gain	*p*-value
No. (%)	59 (9.0)	102 (15.6)	424 (64.8)	49 (7.5)	20 (3.1)	
Age, years	67.4±12.6	66.6±11.8	66.1±13.1	71.4±11.5	66.9±15.8	0.10
Female gender, %	20 (33.9)	43 (42.2)	161 (38.0)	19 (38.8)	9 (45.0)	0.83
BMI at admission, kg/m^2	24.22±4.22	23.82±3.37	23.76±3.07	23.24±3.08	21.09±3.14	**<0.01**
Initial BMI distribution, %						**0.02**
<18.5 kg/m^2	3 (5.1)	5 (4.9)	18 (4.2)	3 (6.1)	3 (15.0)	
18.5-22.9 kg/m^2	21 (35.6)	36 (35.3)	152 (35.8)	21 (42.9)	13 (65.0)	
23.0-24.9 kg/m^2	12 (20.3)	26 (25.5)	118 (27.8)	6 (12.2)	0 (0)	
≥25.0 kg/m^2	18 (30.5)	29 (28.4)	123 (29.0)	19 (38.8)	4 (20.0)	
≥30.0 kg/m^2	5 (8.5)	6 (5.9)	13 (3.1)	0 (0)	0 (0)	
Calorie surplus at 3 days after stroke onset (Kcal)	463.6±695.3	594.5±699.6	748.9±659.3	841.5±621.2	899.8±680.2	**<0.01**
Dysphagia	28 (47.5)	21 (20.6)	37 (8.7)	7 (14.3)	4 (20.0)	**<0.001**
Type of meals at 3 days after stroke onset						
General diet	29 (49.2)	78 (76.5)	367 (86.6)	42 (85.7)	16 (80.0)	**<0.001**
Tube feeding	26 (44.1)	18 (17.6)	30 (7.1)	6 (12.2)	3 (15.0)	
Fasting	4 (6.8)	6 (5.9)	27 (6.4)	1 (2.0)	1 (5.0)	
Cardiovascular risk factor						
Prior ischemic stroke	11 (18.6)	14 (13.7)	56 (13.2)	8 (16.3)	2 (10.0)	0.78
Hypertension	36 (61.0)	61 (59.8)	253 (59.7)	28 (57.1)	8 (40.0)	0.52
Diabetes	19 (32.2)	33 (32.4)	137 (32.3)	12 (24.5)	3 (15.0)	0.43
Dyslipidemia	17 (28.8)	32 (31.4)	139 (32.8)	8 (16.3)	4 (20.0)	0.15
Smoking	25 (42.4)	30 (29.4)	148 (34.9)	20 (40.8)	8 (40.0)	0.45
Atrial fibrillation	21 (35.6)	28 (27.5)	54 (12.7)	11 (22.4)	5 (25.0)	**<0.001**
Mechanism						**<0.01**
LAA	18 (30.5)	24 (23.5)	129 (30.4)	13 (26.5)	5 (25.0)	
SVO	5 (8.5)	18 (17.6)	115 (27.1)	10 (20.4)	6 (30.0)	
Cardoembolic	23 (39.0)	30 (29.4)	78 (18.4)	10 (20.4)	8 (40.0)	
Undetermined	9 (15.3)	19 (18.6)	67 (15.8)	12 (24.5)	0 (0)	

Other determined	4 (6.8)	11 (10.8)	35 (8.3)	4 (8.2)	1 (5.0)	
Hospital duration, days	15.2±6.5	10.8±5.7	8.3±4.3	9.4±5.4	8.8±5.1	**<0.001**
Initial neurological severity, median (IQR)	8 (3,13)	3.5 (1,7)	2 (1,5)	3 (1.5, 4.5)	4 (2, 8)	**<0.001**
NIHSS, 0-7	29 (49.2)	78 (76.5)	371 (87.5)	42 (85.7)	15 (75.0)	**<0.001**
NIHSS, 8-14	16 (27.1)	14 (13.7)	34 (8.0)	5 (10.2)	3 (15.0)	
NIHSS, ≥15	14 (23.7)	10 (9.8)	19 (4.5)	2 (4.1)	2 (10.0)	
Comorbid disease	11 (18.6)	12 (11.8)	41 (9.7)	3 (6.1)	3 (15.0)	0.20
Chronic renal failure	2 (3.4)	1 (1.0)	4 (0.9)	0 (0)	0 (0)	0.43
COPD	0 (0)	0 (0)	4 (0.9)	1 (2.0)	1 (5.0)	0.21
Liver cirrhosis	2 (3.4)	3 (2.9)	7 (1.7)	1 (2.0)	0 (0)	0.79
Cancer	8 (13.6)	9 (8.8)	26 (6.1)	2 (4.1)	2 (10.0)	0.23
Laboratory						
White Blood Cell	8483±2873	7585±2643	7657±2657	7155±2247	8068±2618	0.09
Hemoglobin, g/dL	13.5±2.2	13.6±1.9	13.6±2.0	13.3±1.9	13.3±1.9	0.66
Hematocrit, g/dL	40.1±6.1	40.6±5.0	40.4±5.5	39.3±5.4	37.9±7.8	0.21
FBS, mg/dL	117.9±38.1	108.1±35.0	106.3±35.0	105.7±28.5	105.9±33.9	0.20
HbA1c, %	6.5±1.2	6.4±1.3	6.4±1.3	6.3±1.1	6.2±1.4	0.78
LDL, mg/dL	100.8±33.0	94.6±38.5	104.6±36.2	98.2±38.1	115.2±51.3	0.06
Total cholesterol, mg/dL	165.5±41.8	169.1±35.0	175.7±38.9	170.0±42.9	186.4±64.1	0.12
Triglyceride, mg/dL	112.2±62.3	113.8±56.9	121.4±60.5	103.9±42.3	102.9±57.2	0.16
Albumin,	3.5±0.5	3.7±0.5	3.7±0.5	3.5±0.5	3.5±0.5	0.12
Prothrombin Time	1.05±0.21	0.99±0.13	1.00±0.26	1.03±0.20	1.04±0.09	0.42
aPTT	34.28±10.78	30.91±7.94	32.34±15.09	30.65±4.08	30.86±4.85	0.70
Systolic BP, mmHg	149±29	153±29	152±28	145±25	148±28	0.40
Diastolic BP, mmHg	82±13	88±15	85±17	81±14	80±12	0.06
Type of Insurance						0.73
Health Insurance	54 (91.5)	100 (98.0)	411 (96.9)	47 (95.9)	20 (100.0)	
Medicaid	4 (6.8)	1 (1.0)	11 (2.6)	2 (4.1)	0 (0.0)	
Not insured	1 (1.7)	1 (1.0)	2 (0.5)	0 (0.0)	0 (0.0)	

Abbreviation: BMI, Body mass index; FBS, Fasting blood sugar; LDL, Low density lipoprotein; HDL, High density lipoprotein;
aPTT, activated prothrombin time; LAA, Large artery atherosclerosis; SVO, Small vessel occlusion; BP, Blood pressure; IQR, Interquatile ratio; NIHSS, National Institutes of Health Stroke Scale

No. (%) or mean±SD. *p* Values were calculated by $\chi 2$ test for trend in proportion

Figure 3-2. The types and proportions of weight-change groups in acute ischemic stroke during admission

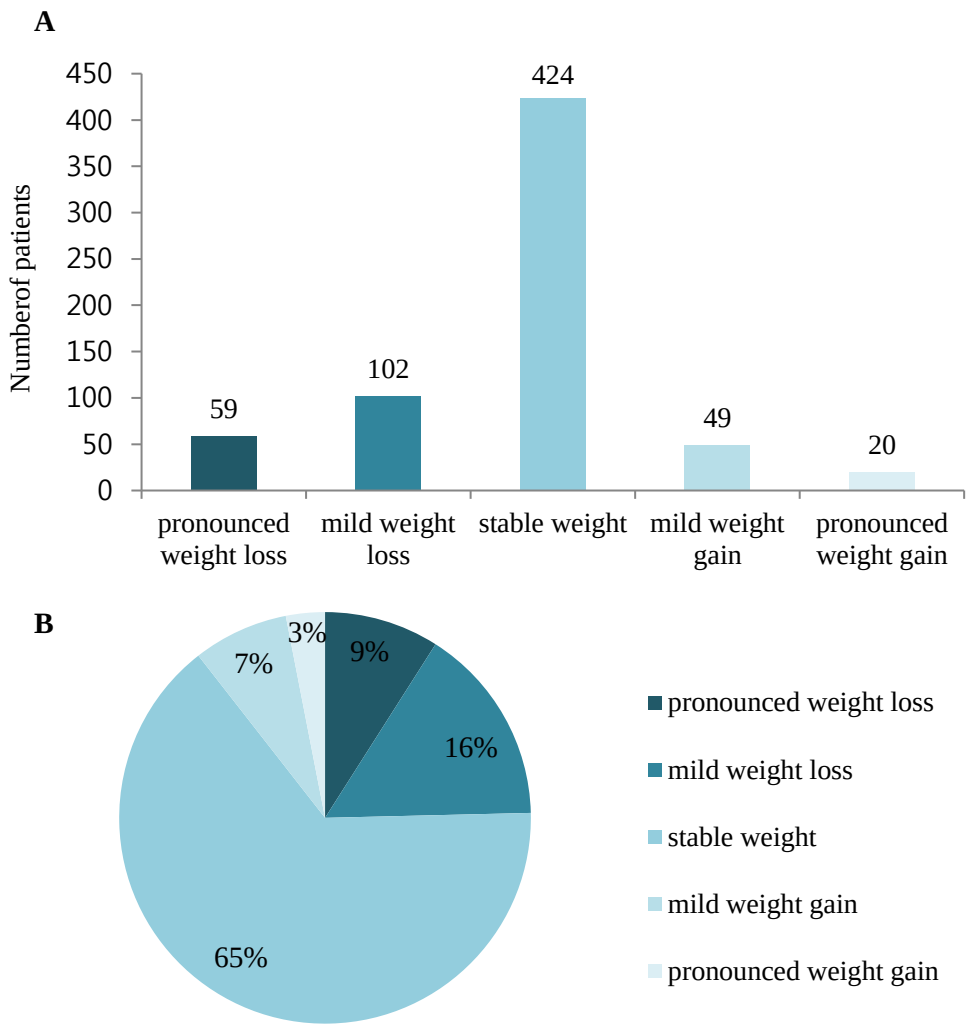

Table 3-2. Effect of weight changes on short-term outcomes (compared to favorable 3-month mRS)

Variables	OR	95% CI	*P*-value
Age, per 1 years	1.04	1.01-1.06	**<0.01**
Hospital duration, per 1 days	1.09	1.04-1.14	**<0.001**
BMI at admission, per 1 kg/m^2	0.90	0.83-0.97	**<0.01**
Type of meals at 3 days after stroke onset			
General diet	reference	reference	reference
Tube feeding	3.12	1.34-7.28	**<0.01**
Fasting	1.45	0.27-7.81	0.67
Initial neurological severity			
NIHSS at admission, 0-7	reference	reference	reference
NIHSS at admission, 8-14	5.29	2.79-10.03	**<0.001**
NIHSS at admission, ≥ 15	3.97	1.51-10.40	**<0.01**
Weight-change group			
Stable weight	reference	reference	reference
Pronounced weight loss, >0.1 kg/baseline BMI-unit	**2.43**	**1.12-5.25**	**0.02**
Mild weight loss, 0.05-0.1 kg/baseline BMI-unit	1.31	0.71-2.40	0.39
Weight gain, ≥0.05 kg/baseline BMI-unit	0.57	0.25-1.31	0.19

Adjusted for age, gender, hypertension, diabetes, dyslipidemia, smoking, atrial fibrillation, stroke subtype, hospital days, comorbid disease, BMI at admission, caloric surplus at 3 days after stroke onset, type of meals at 3 days after stroke onset, Initial neurological severity and weight change.

Abbreviation: BMI, Body mass index; mRS, modified Rankin Scale; OR, Odds Ratios; CI, confidence intervals; NIHSS, National Institutes of Health Stroke Scale

We conducted the binary logistic regression analysis to confirm the impact of weight change levels on the short-term functional outcome. When compared to the stable weight group, the pronounced weight loss group had a 2.43-fold (95% CI 1.12-5.25) risk of having unfavorable outcomes after adjusting for age, gender, hypertension, diabetes, dyslipidemia, smoking, atrial fibrillation, caloric surplus at 3days after stroke onset, type of meals 3 days after stroke onset, stroke subtypes, hospital days, comorbid diseases, BMI on admission and INS. As the weight changed from pronounced weight loss to weight gain, the risk of having an unfavorable outcome decreased (mild weight loss group, OR 1.31, 95% CI 0.71-2.40; mild and pronounced weight gain group, OR 0.57, 95% CI 0.25-1.31) (Table 3-2).

In addition, to clarify the relationships between the impacts of weight change and the short-term functional outcomes, we evaluated further analyses using other definitions of weight change, such as a gain or loss of more than 1 kg or 0.5 kg/m^2 BMI-unit. The pattern of significance remained in this analysis (Table 3-3).

Figure 3-3. Distribution of groups of weight-change after dichotomizing modified Rankin scales at 3 months after stroke onset

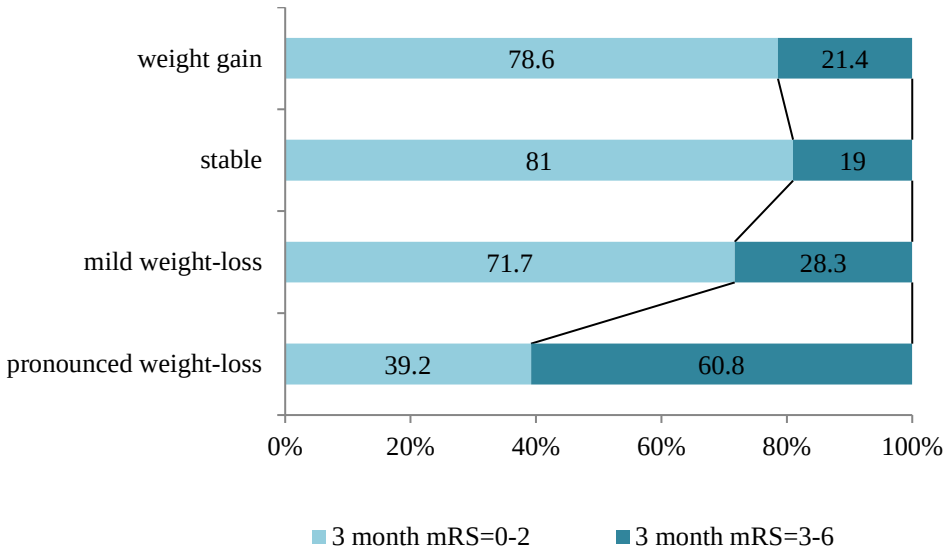

Table 3-3. Relative risks for unfavorable short-term outcomes using other definitions of weight change

Weight-change group (n=654)	OR	95% CI	*P*-value
Weight-change method I, kg			
Stable weight, change ≤±1 kg	reference	reference	reference
Pronounced weight loss, > -2 kg	2.38	1.15-4.93	**0.020**
Mild weight loss, -1~-2 kg	1.40	0.75-2.61	0.288
Weight gain, >1kg	0.73	0.34-1.55	0.406
Weight-change method II, kg/m^2			
Stable weight, change ≤ ±0.5 kg/m^2	reference	reference	reference
Pronounced weight loss ≥ 1 kg/m^2	2.40	1.06-5.46	**0.036**
Mild weight loss, 0.5-1 kg/m^2	1.34	0.70-2.57	0.376
Weight gain, >0.5 kg/m^2	0.67	0.28-1.63	0.381

Adjusted for age, gender, hypertension, diabetes, dyslipidemia, smoking, atrial fibrillation, stroke subtype, hospital days, comorbid disease, BMI at admission, caloric surplus at 3 days after stroke onset, type of meal at 3 days after stroke onset, Initial neurological severity and weight change.

Abbreviation: BMI, Body mass index; mRS, modified Rankin Scale; OR, Odds Ratios; CI, confidence intervals

Discussion

The main findings of this study were as follows: (1) patients with pronounced weight loss during AIS had unfavorable short-term functional outcomes compared to patients with stable weight and (2) approximately a quarter of the patients experienced weight loss during the relatively short average hospital stay of 9 days in our stroke registry. Therefore, we suggest that it is critical to monitor weight change during the AIS period in terms of treating nutritional imbalance.

It is noticeable that weight loss after stroke occurred more often than we predicted. In a prior population-based study, weight loss >3 kg was observed in 24% of stroke patients after 4 months and in 26% 1 year later.[55] Further, among 4,360 subjects with coronary artery disease, a quarter of patients (24.9%) reported weight loss at 3 months.[54] In this study, we should emphasize that weight loss during AIS was not intentional but observational consequences. Unlike intentional weight loss, observational weight loss may be related to poor functional outcomes.[61]

The reasons for the pronounced weight loss during the long-term as well as the short-term periods after stroke remain to be determined. The body weight change after stroke might affect the patients' outcome differently than it does healthy individuals. Multifactorial pathomechanisms, including amount of fluid intake, decreased physical activity, sympathetic activation, and systematic inflammation, may contribute to metabolic imbalances. Since this study was not intended for severely critical patients in an intensive care unit (ICU), it was unavailable to collect exact data about the fluid balance intake. However, based on the prior studies, the recorded fluid balances were thought to be unreliable.[62,63] Calculated fluid balances are not predictive indicators of actual weight changes in critically ill subjects because other factors (fever, parenteral nutrition, and tracheal intubation) leading to unintentional weight loss have been discovered to be essential.[63,64] The net effect of catabolic cascade is an acceleration of tissue destruction, resulting in muscle wasting and overall unintentional weight loss.[56] Prior studies supporting the "obesity paradox" have demonstrated that obese patients might have an energy reservoir under some

catabolic status, and consequently, obesity might be correlated with better outcomes.[15, 65] Despite BMI being commonly used to evaluate obesity, it has received a lot of critique regarding its accuracy to define obesity. Because BMI is an aggregate of lean mass and body fat, estimating body composition is significant.[66] In a previous study, higher lean mass index was clearly protective. Because lean mass was known to be related to muscle power and cardiorespiratory fitness, "lean mass index" might play a crucial role in "obesity paradox".[67] However, little is known about the pathophysiological changes that arise in the skeletal muscle after an index stroke. Numerous data suggest that inflammatory cytokines, such as tumor necrosis factor, may provoke tissue degradation and promote weight reduction.[68, 69]

Energy malnutrition in elderly and critically ill patients is a crucial parameter of high morbidity and mortality.[70] Current guidelines suggest that a calorie and protein intake closer to the recommended amounts during the early phase in critical illnesses are associated with a better clinical outcome.[71] In addition, despite the fact that there is limited evidence that nutritional intervention may enhance short-term outcomes, recent guidelines recommended that it is reasonable to perform a nutritional evaluation for patients with AIS.[50] In this study, short-term weight loss after stroke is determined by complex mechanisms such as nutritional deficiency, eating difficulties, hemodynamic status, stroke severity and underlying comorbid diseases. Therefore, we should be cautious in indicating weight loss as malnutrition per se. However, there is no "gold standard" in figuring out nutritional status because there is no universally accepted definition of malnutrition.[72] Thus, overall weight loss is considered to be a gross indicator of a nutritional deficit.[59]

The strength of this study is that it is the first report to focus on the importance of weight loss in patients with AIS. Weight change during the recovery after stroke has been relatively overlooked despite its importance. We suggest that a lot of patients with AIS experienced unintentional weight loss, even during a brief hospital period, and weight change should be considered as a treatment target to detect unintentional weight loss related to possible malnutrition. However, there are

some limitations. First, this is a retrospective, observational, single-center study. Second, in cases of changing patients' neurological status, modalities to obtain weight and height might be different. However, except for a few cases, since body weight was measured using a calibrated scale with identical protocol, the modalities to measure body weight would be matched in the same individuals. Third, patients with pronounced weight loss had frequent dysphagia. However, even if patients had dysphagia on initial assessment, sufficient calories were provided through the Levin tube, as needed. Fourth, weight change is associated with several factors including dysphagia, hospitalization, and stroke severity. Fifth, we did not obtain fluid intake and biomarkers such as serum albumin and total cholesterol levels that can reflect nutritional status. However, a previous study demonstrated that the recorded fluid balances were considered unreliable and the serum albumin and total cholesterol levels have limited evidence because they fluctuated depending on acute phase reactants and statin use. Sixth, preexisting comorbid disease may affect stroke outcome. However, there had been no statistically significant differences among the weight-change groups. Additionally, although preexisting diseases might influence the long-term outcomes, they may have relatively fewer effects on the short-term outcomes. Finally, because of the short duration of admission, we predefined weight-change more strictly than previous reviews. Regarding the short length of hospital stay, we think that even a very mild weight change might be crucial in this analysis. To overcome the limitations of our method, we also conducted additional analyses using other methods and confirmed that the pattern of significance still remained.

In conclusion, weight loss during AIS is common and appears to be related to unfavorable short-term functional outcomes. We suggest that appropriate nutritional support should be considered as a component of medical treatment, and weight loss should be monitored as a parameter of malnutrition.

Summary

In this study, both pre-stroke and post-stroke metabolic conditions are associated with short-term functional outcomes after stroke. Since prediction of outcome after stroke may help physicians provide an effective management plan, controlling these modifiable conditions is crucial. As mentioned, although nutritional imbalance (malnutrition or over-nutrition) and glucose intolerance are the main contributors of glucometabolic disorders, its significance is undervalued. In this regard, although further large, well-designed studies are warranted, our results show that (1) although obesity was associated with a favorable short-term outcome after stroke, INS might be a more significant predictor. (2) GA level might have a better prognostic importance to predict the 3-month outcome after stroke than the HbA1c level. (3) Clinical nutritional supplement should be considered as an element of the medical management after stroke, suggesting a novel point of view in managing patients with AIS.

The increase in the risk for cerebral ischemia observed in patients with metabolic syndrome may suggest the potential capacity of expanding the treatment area and improving the stroke prognosis. In the future, specific therapeutic treatments targeting individual metabolic abnormalities may offer additional benefit in stroke prognosis. In this context, constant effort should be given to elucidate the pathomechanism of stroke related to metabolic conditions in AIS.

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국문초록

배경 및 목적: 뇌졸중으로 인한 사망률이 감소함에도 불구하고, 인구의 고령화로 인해 뇌졸중과 관련된 사회경제적 부담은 증가하고 있다. 뇌졸중의 예후에 있어 조절 가능한 인자를 찾고 그 영향력을 파악하는 것은 매우 중요하다. 이러한 관점에서, 뇌졸중과 관련된 대사적 상태는 뇌졸중의 예후를 결정짓는 매우 잘 알려진 예후인자이다. 몇 개의 대사성 지표 가운데, 영양 불균형 (영양부족이나 과영양상태) 과 당불내성은 당대사질환의 주요 요소임에도 불구하고, 그 중요성은 간과되어왔다. 그러므로, 우리는 이 연구를 통해 뇌졸중 전 비만도, 뇌졸중 전 당 조절 정도, 그리고 뇌졸중 후 영양 보충이 뇌졸중의 중증도 와 예후에 어떠한 영향력을 가지고 있는지 연구하고자 하였다.

방법: (1) 2002년 10월부터 2019년 10월까지 서울대학교 병원에 급성 뇌경색으로 입원한 총 2,826명의 환자가 등록되었다. 비만도와 입원 초기 뇌경색 중증도 와 단기 뇌경색 예후를 분석하기 위해, 비만도는 체질량지수를 이용하여 정의하였다. (2) 2016년 5월과 2019년 12월 사이 한림대학교 강동성심병원과 춘천성심병원에 급성 뇌경색으로 입원한 1,347명이 이 연구에 포함되었다. 뇌졸중 전 당 조절도 와 뇌졸중 예후를 파악하기위해 당화혈색소에 더하여 당화 알부민을 측정하였다. (3) 2010년 3월부터 2013년 5월까지 서울대학교 병원에 급성 뇌경색으로 입원한 654명이 이 연구에 포함되었다. 뇌졸중 후 체중변화가 뇌졸중의 예후에 어떠한 영향을 미치는지를 평가하기 위해, 체중변화는 체질량지수 단위 기준 > 0.05 kg 의 체중 증가 또는 감소로 정의하였다.

결과: (1) 입원 시 체질량지수가 가장 낮은 환자들에 비하여 체질량지수가 가장 높은 환자들이 중증도 이상의 뇌경색으로 발현할

오즈비가 0.3배였다. (2) 당화 알부민 수치가 높은 환자들이 (당화알부민≥16%) 당화알부민 수치가 낮은 환자들에 비하여, 뇌졸중 후 3개월째 단기 예후가 1.4배 나쁜 결과를 보였고, 당화혈색소에 비하여 당화알부민은 뇌졸중 단기 예후와 더 유의한 관련성을 보였다. (3) 뇌졸중 후 비교적 짧은 입원기간 동안의 체중 감소가 예상보다 흔했으며, 체중변화가 별로 없는 집단에 비하여, 입원중 유의한 체중 감소는 2.4배 나쁜 뇌졸중 예후와 관련되었다.

결론: 뇌졸중 전후의 대사적 상태는 뇌졸중의 예후에 밀접한 관련이 있다. 그러므로 의료인은 뇌졸중의 재발을 예방하기 위해 뇌졸중 전 환자의 조절가능한 뇌졸중 위험인자를 충분히 조절해주고, 뇌졸중 발생 후에는 체중감소가 일어나지 않도록 모니터링하여야 한다. 또한 적절한 영양 공급을 하는 것이 뇌졸중의 내과적 치료의 중요한 요소로 고려되어야 한다.

주요어: 체질량지수, 당화 알부민, 당화혈색소, 비만, 뇌경색, 예후, 대사질환, 영양상태

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