RESEARCH PAPER

Obesity-stroke paradox and initial neurological severity

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ABSTRACT

Background and purpose An obesity paradox in patients with stroke has been documented. However, although the initial neurological severity (INS) is generally the most important prognostic factor, the impact of this paradox has not been considered in most previous studies. We sought to investigate the impact of obesity on INS in patients with ischaemic stroke and to investigate whether it is a significant risk factor for short-term outcomes.

Methods A total of 2670 patients from Seoul National University Hospital with ischaemic stroke were enrolled from October 2002 to May 2013. Baseline information, including body mass index (BMI) and INS, was collected at admission. Associations between obesity and INS were analysed. In addition, we evaluated the effect of BMI on modified Rankin Scale (mRS) 3 months after stroke onset.

Results Among the 2670 patients, patients whose BMI levels were higher than the chosen reference level had reduced risks of moderate to severe INS (Q2: OR, 0.65; 95% CI 0.49 to 0.87; Q3: OR, 0.48; 95% CI 0.35 to 0.65; Q4: OR, 0.39; 95% CI 0.28 to 0.54; and Q5: 0.31; 95% CI 0.22 to 0.44). In addition, of the 703 patients with available 3-month mRS patients with higher BMI levels seem to have had more favourable outcomes. Such associations disappeared after adjusting for INS.

Conclusions In our study, although obesity was associated with better short-term functional outcomes, INS might be a more important prognostic factor. Therefore, initial status should also be considered when considering an 'obesity paradox' in chronic diseases.

INTRODUCTION

Although mortality due to stroke has been on the decline recently, it remains a major cause of long-term disability and associated enormous socioeconomic declines.[1] Although obesity is known to be associated with risk factors for vascular disease and overall mortality,[2–4] some reports have indicated that there is an inverse relationship between obesity and clinical outcomes in patients with cardiovascular disease. This paradoxical phenomenon is commonly referred to as an 'obesity paradox'.[5–8] This paradoxical relationship has been identified not only in cardiovascular diseases but also in chronic diseases such as chronic obstructive pulmonary disease, peripheral arterial disease, diabetes, chronic kidney disease and malignancy.[9–12] Our previous studies have shown that overweight individuals and individuals with mild to moderate obesity have a lower risk of long-term mortality after either haemorrhagic or ischaemic stroke.[13–15] However, this paradoxical phenomenon seems to be limited in scope in our data. An inverse relationship between a patient's body mass index (BMI) and mortality is not always clear. The worst outcomes have emerged at both the lowest and the highest BMI levels. Unlike in standard descriptions of the obesity paradox, severe obesity was not associated with a protective effect. In addition, the clinical outcome after stroke is determined by multiple, complex mechanisms. Among these, initial neurological severity (INS) is generally the most important prognostic factor, but it has not been considered significantly in most previous studies of this paradox.

Therefore, we sought to investigate the impact of obesity on INS in patients with ischaemic stroke and to investigate whether it is a significant risk factor for short-term outcomes.

METHODS

Study population

We enrolled a consecutive series of patients with acute ischaemic stroke or transient ischaemic attack (TIA) who were admitted within 7 days of symptom onset to our stroke centre from October 2002 to May 2013 inclusive into our prospective stroke registry system. Initially, we included a total of 3324 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 2670 patients participated in this study. In Analysis II, we evaluated the effects of BMI on short-term outcomes (3-month mRS). In our registry system, the 3-month mRS was collected from March 2010; a total of 703 patients who had records concerning the 3-month mRS were entered into this analysis.

All patients received standard and optimal medical therapy during hospitalisation. The institutional review board of the Seoul National University Hospital (1312-066-541) 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. Baseline demographic and clinical information was collected during the admission period as follows: age at onset, gender, hypertension (previous use of antihypertensive medication, systolic blood pressure

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>140 mm Hg or diastolic blood pressure >90 mm Hg at discharge), diabetes (previous use of anti-diabetic medication under the diagnosis of diabetes, 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 habit status, history of stroke and history of heart disease before index stroke. Body weight and height were measured at admission. In cases of severe stroke, we measured body weight using an under-bed scale and height using a tapeline. BMI was calculated as the weight (kg) divided by the square of the height (m).

INS was estimated using the National Institute of Health Stroke scale (NIHSS) score at admission. Since NIHSS scores were not normally distributed, we classified them as follows: 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.[16] We classified stroke subtypes based on the method reported in the Trial of Org 10 172 in Acute Stroke Treatment (TOAST). The short-term outcome was estimated using the mRS at 3 months after stroke onset. We evaluated the distribution of BMI quintiles after dichotomising mRS at 3 months after stroke onset (favourable outcome: 3-month mRS 0–2; unfavourable outcome: 3-month mRS 3–6).

Statistical analysis

The distribution of demographic, clinical, laboratory and stroke subtype data according to the stroke severity (mild vs moderately severe) was analysed using a χ^2 test, Student's t test or one-way analysis of variance (ANOVA), as appropriate. The trend in baseline data was also calculated using the χ^2 test for trends in proportion or an ANOVA. We also used the Kruskal-Wallis test for nonparametric analysis. To evaluate the impact of obesity status itself, we did not use the predetermined guidelines for BMI such as the WHO international classification recommendations or the guidelines for an Asian-Pacific population. Instead, obesity status as a categorical variable was established by dividing the BMI into 5 levels, according to the quintiles of BMI (Q1, <21.2; Q2, 21.2–23.0; Q3, 23.1–24.5; Q4, 24.6–26.2; and Q5, ≥26.3 kg/m^2). The lowest BMI category was used as a reference level. In Analysis I, the associations between the BMI or obesity status and the INS were estimated using binary and ordinal logistic regression analyses. For the dependent variables, mild stroke (NIHSS 0–7) was used as a reference group in the binary and ordinal logistic regression analysis. In Analysis II, we evaluated the associations between BMI or obesity status and functional outcomes at 3 months after stroke onset.

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

RESULTS

Analysis I: BMI and INS

Among the 2670 participants, the mean age was 65.9±12.4 years, and 38.1% were women. The baseline demographic and clinical characteristics are shown in table 1. A total of 2099 patients (78.6%) were included in the mild stroke group. Compared with patients with mild stroke, patients with moderate to severe stroke at admission were relatively older and had some prevalent conventional vascular risk factors, such as prior ischaemic stroke, hypertension and atrial fibrillation. In contrast, patients with mild stroke at admission had frequent small vessel occlusion as a stroke aetiology and tended to be included in the higher BMI categories. The means±SD of the BMI values were 24.2±3.2 in the mild stroke group and 22.6±3.4 in the moderate to severe stroke group.

After categorising 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 at admission, and thin patients were more likely to have moderate to severe stroke at admission. Figure 1 shows the distribution of INS according to the BMI levels. Patients with higher BMI levels had lower NIHSS scores at admission (p for trend <0.001; figure 1). When compared with the lowest BMI group, the highest BMI group had a reduced risk of having moderate to severe stroke at admission (OR 0.31; 95% CI 0.22 to 0.44). As the severity of obesity increased, the risk of having moderate to severe stroke decreased (Q2: OR, 0.65; 95% CI 0.49 to 0.87; Q3: OR, 0.48; 95% CI 0.35 to 0.65; Q4: OR, 0.39; 95% CI 0.28 to 0.54). To confirm this result, we further conducted an ordinal logistic regression analysis. In the ordinal logistic regression analysis, this pattern of significant association remained (table 2): a higher BMI level indicated greater relevance.

In addition, analyses of the effects of obesity on stroke subtype suggested that obese patients were significantly linked to the stroke subtype of small vessel occlusion (see online supplementary tables 1 and 2 and online supplementary figure 1).

Analysis II: BMI and 3-month mRS

Of the 703 included participants, 176 (25.0%) patients had poor functional outcomes. The patients with poor functional outcomes were more likely to be older (p<0.001) and to be female (p=0.02). Those with higher BMI levels seemed to have more favourable short-term outcomes (p for trend <0.01; figure 2). In the binary logistic regression, being overweight or obese was independently associated with better outcomes. However, after adjusting for INS, this association disappeared, except at the BMI level of 24.6–26.2 (table 3).

DISCUSSION

In summary, we found that patients with higher BMI levels were more likely to have mild strokes at admission. In addition, we found that patients with higher BMI levels also had a lower mRS at 3 months after stroke onset, in concurrence with previous reports. However, in a model adjusted for INS, this association did not maintain its significance. Therefore, we suggest that INS might be a more powerful factor than BMI levels.

Prior studies supporting an 'obesity paradox' have evaluated the associations between obesity and mortality. In a large cohort study of 1203 patients with heart failure, obesity was associated with a trend towards improved survival.[6] In a prospective Greek study in 2785 patients with stroke, who were followed for up to 10 years, obesity was associated with better outcomes.[17] Another study examined a database of 17 648 patients with stroke, reporting that obesity was associated with lower mortality in elderly overweight and obese patients.[18] All of these studies supporting the 'obesity paradox' analysed the relationship between BMI and mortality. However, since the clinical outcome after stroke is determined by complex mechanisms, we assessed it from different perspectives. As mentioned above, we suggest that obese patients may have less severe strokes initially and therefore have better functional outcomes.

It then remains to be determined why patients with higher BMI levels presented initially with mild stroke. It is noteworthy

Table 1 Baseline characteristics according to the initial stroke severity

	Mild (NIHSS 0–7)	Moderate to severe (NIHSS≥8)	p Value
No. (%)	2099 (78.6)	571 (21.4)	
Age, years	65±12	69±12	<0.001
Female sex, %	781 (37.2)	237 (41.5)	0.06
Cardiovascular risk factor			
Prior ischaemic stroke	397 (18.9)	117 (20.5)	0.40
Hypertension	1329 (63.3)	366 (64.1)	0.73
Diabetes	693 (33.0)	177 (31.0)	0.36
Dyslipidemia	545 (26.0)	119 (20.8)	0.01
Smoking	765 (36.4)	177 (31.0)	0.02
Atrial fibrillation	260 (12.4)	190 (33.3)	<0.001
Laboratory			
White cell count	7671±2698	8937±3284	<0.001
Haemoglobin, g/dL	13.7±1.9	13.3±2.1	<0.01
Haematocrit, g/dL	40.4±5.4	39.2±6.0	<0.001
Fasting blood sugar, mg/dL	111.1±38.6	120.2±43.4	<0.001
HbA1c, %	6.5±2.3	6.3±1.2	0.04
Low-density lipoprotein, mg/dL	106.7±39.2	100.3±53.3	<0.01
Total cholesterol, mg/dL	178.7±38.8	171.0±44.1	<0.001
High-density lipoprotein, mg/dL	45.3±15.0	46.8±22.0	0.14
Triglyceride, mg/dL	129.2±75.0	109.6±58.8	<0.001
Prothrombin time	1.05±0.48	1.10±0.36	0.01
Activated partial thromboplastin time	36.34±17.40	36.17±12.36	0.84
Systolic blood pressure, mm Hg	152±27	148±28	<0.01
Diastolic blood pressure, mm Hg	86±16	84±16	<0.001
Mechanism			<0.001
Large artery atherosclerosis	612 (29.2)	164 (28.7)	
Small vessel occlusion	628 (29.9)	35 (6.1)	
Cardioembolic	340 (16.2)	227 (39.8)	
Undetermined	416 (19.8)	121 (21.2)	
Other determined	103 (4.9)	24 (4.2)	
BMI, kg/m^2	24.1±3.2	22.6±3.4	<0.001
BMI quintiles, median (IQR)	24.1 (22.2, 26.1)	22.5 (20.4, 24.5)	<0.001
Q1 (<21.2)	361 (17.2)	195 (34.2)	
Q2 (21.2–3.0)	420 (20.0)	141 (24.7)	
Q3 (23.1–24.5)	419 (20.0)	102 (17.9)	
Q4 (24.6–26.2)	437 (20.8)	72 (12.6)	
Q5 (≥26.3)	462 (22.0)	61 (10.7)	

N (%) or mean±SD. p Values were calculated by the χ^2 test for trend in proportion.BMI, body mass index; HbA1c, glycated haemoglobin; NIHSS, National Institute of Health Stroke scale; Q, quintiles.

that patients with higher BMI levels were more likely to have strokes due to small vessel occlusion, whereas lean patients were more likely to have strokes due to cardioembolism. Lacunar infarction is known to be related to diabetes and hypertension. However, the relationship between obesity and stroke subtype has not yet been firmly established.[19 20] Our results suggest that increased BMI levels may yield an unknown mechanism for favouring the development of small-vessel disease. In the Hisayama study, high BMI was a potent risk factor for incident lacunar infarction in a Japanese population.[21] In addition, recent studies have reported that obese patients were found to have lower levels of tumour necrosis factor and other inflammatory cytokines.[22] Adipose tissue is believed to produce a tissue necrosis factor receptor.[23] Furthermore, lacunar infarction showed significantly lower plasma levels of tumour necrosis factor-α, interleukin-6 and interleukin-1β.[24]

We may assume that patients with higher BMI levels may more often use preventive drugs and be under control because of their cerebrovascular risk factors. It has been reported that higher BMI is associated with the increased use of guideline-recommended medical treatment such as aspirin, inhibitors of the renin-angiotensin system and lipid-lowering therapy and invasive managements.[25] Another point of note is that socioeconomic status is related to attention to health. According to the National Health and Nutrition Examination Survey in the USA, the prevalence of obesity increases as income decreases.[26] However, in developing countries, the more affluent and/or those with a higher educational status have a tendency to be more likely to be obese.[27] In Korea, the association between BMI and socioeconomic status becomes largely mixed for men and mainly negative for women.[28] Therefore, people with a higher socioeconomic status tend to be overweight or mild obese.

The strength of this study is that it is the first report reviewing the 'obesity-stroke paradox' in terms of INS. However, there are some caveats to this study. First, since this is a retrospective observational study, unknown factors might have confounded our results. Second, we obtained only the 3-month mRS, which

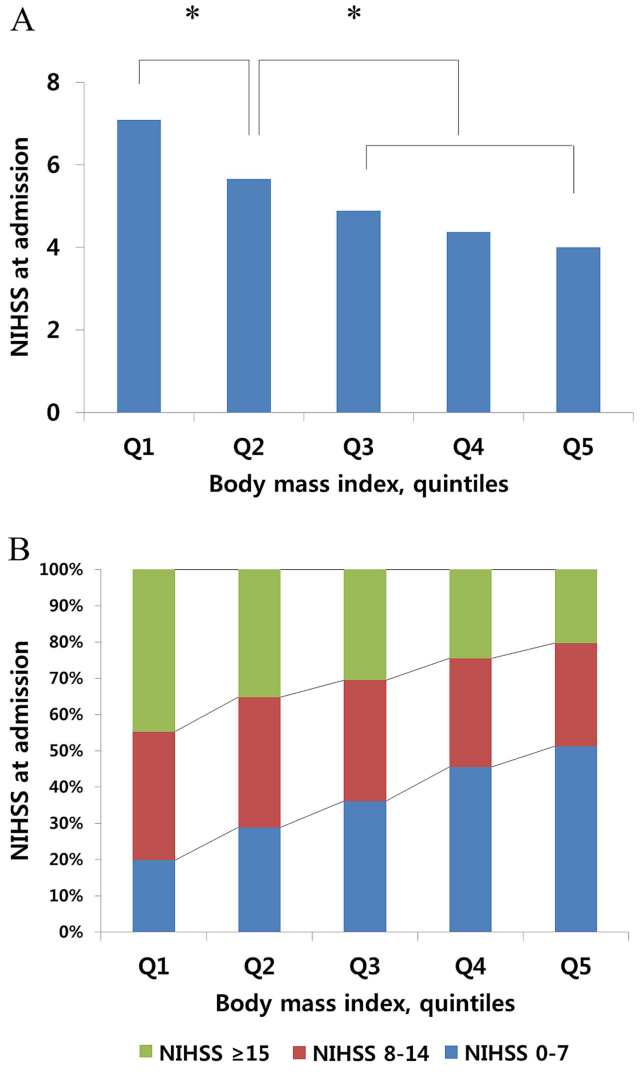

Figure 1 Body mass index (BMI) and initial stroke severities. Association between BMI and initial neurological severity (A) and Distribution of NIHSS according to the levels of BMI quintiles at the onset of stroke (B). NIHSS, National Institute of Health Stroke scale; BMI, body mass index; Q, quintiles.

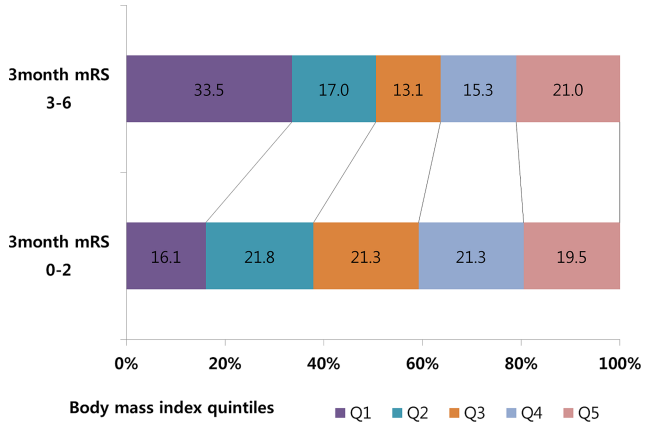

Figure 2 Distribution of BMI quintiles after dichotomising modified Rankin scales at 3 months after stroke onset. BMI, body mass index; mRS, modified Rankin Scale; Q, quintiles.

Table 2 Binary and ordinal logistic regression analysis for moderate to severe stroke after being categorised into initial stroke severity (compared to mild stroke severity)

	OR	95% CI	p Value
Binary logistic regression (mild vs moderate to severe)			
BMI Q5 (≥26.3)	0.31	0.22 to 0.44	<0.001
Q4 (24.6–26.2)	0.39	0.28 to 0.54	<0.001
Q3 (23.1–24.5)	0.48	0.35 to 0.65	<0.001
Q2 (21.2–23.0)	0.65	0.49 to 0.87	<0.01
Q1 (<21.2)	reference	reference	reference
Ordinal logistic regression			
BMI Q5 (≥26.3)	0.31	0.22 to 0.44	<0.001
Q4 (24.6–26.2)	0.39	0.28 to 0.54	<0.001
Q3 (23.1–24.5)	0.48	0.35 to 0.65	<0.001
Q2 (21.2–23.0)	0.65	0.49 to 0.87	<0.01
Q1 (<21.2)	reference	reference	reference

Adjusted for gender, age, dyslipidemia, smoking, atrial fibrillation, serum white blood cell, serum haematocrit, serum fasting blood sugar, diastolic blood pressure and stroke subtype.
BMI, body mass index; Q, quintiles.

did not firmly reflect the mortality data. Nevertheless, our objective was to evaluate the association between BMI and INS. Third, we did not obtain information on prestroke medication history. Fourth, BMI is not a direct measurement of body composition, such as body fat composition, waist-hip ratio or abdominal circumference, which may act more effectively than BMI. Finally, the mean BMI is relatively low compared with that reported previously. Owing to the sample being of Korean ethnicity, it is unclear whether it could be generalised to other ethnic groups.

Collectively, the 'obesity-stroke paradox' seems to be limited, at least in patients with ischaemic stroke. However, it should be noted that this study addresses some critical issues. Although outcomes after stroke are significantly related to the initial stroke severity, previous studies have not paid enough attention to the NIHSS at admission. Similarly, to fully demonstrate an 'obesity paradox', the initial status should be considered in patients with heart failure or other chronic diseases. In addition, we should recognise that the existing classification of BMI is not

Table 3 Binary logistic regression analysis for unfavourable outcome after being categorised into 3-months mRS (compared with favourable outcome)

	OR	95% CI	p Value
Model 1 BMI Q5 (≥26.3)	0.54	0.30 to 0.99	0.05
Q4 (24.6–26.2)	0.40	0.21 to 0.74	<0.01
Q3 (23.1–24.5)	0.45	0.25 to 0.80	<0.01
Q2 (21.2–23.0)	0.56	0.32 to 0.99	0.04
Q1 (<21.2)	reference	reference	reference
Model 2 BMI Q5 (≥26.3)	0.76	0.39 to 1.49	0.43
Q4 (24.6–26.2)	0.43	0.21 to 0.86	0.02
Q3 (23.1–24.5)	0.60	0.32 to 1.14	0.12
Q2 (21.2–23.0)	0.57	0.30 to 1.07	0.08
Q1 (<21.2)	reference	reference	reference
NIHSS at admission ≥15	17.59	8.20 to 37.73	<0.001
8–14	9.83	5.42 to 17.84	<0.001
0–7	reference	reference	reference

Model 1: Adjusted for gender, age, dyslipidemia, smoking, atrial fibrillation, serum white blood cell, serum haematocrit, serum fasting blood sugar, diastolic blood pressure and stroke subtype.
Model 2: model 1 plus initial neurological severity.
BMI, body mass index; NIHSS, National Institute of Health Stroke scale; Q, quintiles

constant or fully reliable. Since it is too crude for defining normal versus abnormal, the 'normal range of BMI' may not be the right index for determining 'healthy'. In Korea, since the proportion of severely obese patients is too small, the existing BMI categories were not applied. Furthermore, in this study, there was a trend that the BMI increased as the patients' ages decreased (not shown in table). A similar trend was observed in prior studies in patients with ischaemic stroke.[15 29] Therefore, the development of new BMI systems according to race and age might be required.

Contributors S-HL and B-WY devised the original study concept and design. CKK and SJ participated in the acquisition of data. YK and CKK performed statistical analyses. S-HL and B-WY made an intellectual contribution. YK and S-HL interpreted the results and wrote the manuscript.

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