REVIEW

Obesity as a risk factor for cerebrovascular disease

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Abstract. Obesity is widely recognized as a risk factor for coronary artery disease, but opinion is divided regarding whether it is an independent risk factor for cerebrovascular disease; even now there is no common view. In this study, the review sought to focus on a prospective study, but since obesity and non-obesity basically cannot be randomly assigned, randomized controlled trials (RCT) are nonexistent. Accordingly, a cohort study (a method of clinical study in which the obesity group is actively followed up for comparison with the non-obesity group in regard to cerebrovascular disease) was mainly conducted. For reference, retrospective case-control studies are also shown. As a result, most epidemiological surveys on the relation between simple obesity and cerebrovascular disease denied any relation. That is, obesity alone, determined only on the basis of height and weight as shown by BMI (body mass index), etc., cannot be an independent risk factor for cerebrovascular disease; obesity can become a risk factor only when accompanied by hypertension, hyperlipidemia, impaired glucose tolerance, etc. Recently, however, most papers conclude that abdominal obesity is a risk factor for cerebral infarction, provided that there are no data confirming that obesity is a risk factor for hemorrhagic cerebrovascular disease (cerebral hemorrhage and subarachnoid hemorrhage). (Keio J Med 53 (1): 7–11, March 2004)

Key words: obesity, cerebrovascular disease (CVD), risk factor, body mass index (BMI), waist-to-hip circumference ratio (WHR)

Introduction

Obesity is widely recognized as a risk factor for coronary artery disease, but opinion is divided regarding whether it is an independent risk factor for cerebrovascular disease; even now there is no common view. In this study, the review sought to focus on a prospective study, but since obesity and non-obesity basically cannot be randomly assigned, randomized controlled trials (RCT) are nonexistent. Accordingly, a cohort study (a method of clinical study in which the obesity group is actively followed up for comparison with the non-obesity group in regard to cerebrovascular disease) was mainly conducted. For reference, retrospective case-control studies are also shown.

Negative Epidemiological Survey

From 1977 through 1983, Tanaka, *et al.*[1] prospectively studied inhabitants of Shibata City, Niigata Prefecture, who were above 39 years of age, regarding cerebral infarction. In their results they listed aging, hypertension, electrocardiographic high R wave and ST-T change, atrial fibrillation and albuminuria as significant risk factors, but did not list obesity and hyperlipidemia as risk factors.

A study by Wilhelmsen[2] selected 47–55 year-old males at random and conducted a follow-up survey for 11.8 years; he reported that obesity was not a significant risk factor for stroke, though it was a risk factor for coronary artery disease, and that hypertension, smoking and stress were related to stroke.

Also, a follow-up survey of 19,327 inhabitants of Copenhagen from 1976 through 1983 conducted by Boysen, *et al.*[3] revealed that low annual income, smoking, hypertension, diabetes, hypercholesterolemia, ischemic heart disease and atrial fibrillation were related to stroke, and that obesity was not a significant risk factor for stroke.

Konuma[4] examined the role played by obesity in, and other risk factors for, asymptomatic cerebral infarction on MRI. Subjects comprised 75 obese hyper-

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tensives at high risk of cerebral infarction. Regarding results for body mass index (BMI), the MRI-positive and -negative groups had 24.2 ± 3.1 (kg/m^2; $n = 38$) and 23.4 ± 2.9 (kg/m^2; $n = 37$), respectively; that is, no significant difference was observed. Meanwhile, the MRI-positive group had significantly high total serum cholesterol and triglyceride values, and significantly low HDL cholesterol value. On the basis of the above results, the author concluded that hyperlipidemia and hypertension were risk factors for asymptomatic cerebral infarction, and that obesity in itself had no part.

Haapaniemi, *et al.*[5] surveyed risk factors for cerebral infarction in the working-age population, using 506 patients and 345 controls. They concluded that risk factors for cerebral infarction for males were excessive drinking, hypertension, heart disease, smoking, diabetes and past history of migraine; the risk factors for females were excessive drinking, use of oral contraceptives and smoking; obesity was not found to be a risk factor for cerebral infarction in either sex.

Gillum, *et al.*[6] conducted a cohort follow-up survey of 3,652 females and 3,284 males from 1971–1975 through 1992, and reported that while white male BMI showed a U-shaped stroke risk, for black females surprisingly the lowest BMI group showed the highest risk of stroke.

Positive Epidemiological Survey

Hubert, *et al.*[7] analyzed the results of a 26-year follow-up survey of 5,209 inhabitants of Framingham with regard to cardiovascular disease, including stroke, and reported that in females above all, obesity was an independent risk factor for stroke.

Herman, *et al.*[8] conducted a case-control study of the inhabitants of Tilburg, Netherlands, from 1978 through 1981. From an analysis of 132 stroke patients and 239 age- and sex-matched controls, they concluded that hypertension, acute myocardial infarction, arrhythmia, transient cerebral ischemic attack, lack of exercise in spare time, poor education and obesity were risk factors for stroke.

Abbott, *et al.*[9] for 22 years followed up 1,163 nonsmoking Hawaiian males who had no evident risk factors for stroke, including hypertension and diabetes, and reported that the onset rate of thromboembolic stroke conspicuously increased among those with high BMI. This rate was significant even after adjustment for age, systolic blood pressure, blood glucose level, etc. This study is characterized in that they sought to determine the influence of obesity over a long period of time, excluding individuals with other risk factors, such as smoking. While smoking is a risk factor for stroke, it decreases body weight; it is therefore better not to deal with both factors at the same time.

Shinton[10] conducted a case-control study on lifestyle with 125 stroke patients and 198 healthy persons in Birmingham, and concluded that smoking, lack of exercise and obesity (BMI > 25 kg/m^2) were the risk factors for stroke, and that 79% of those cases could have been prevented if all three factors had been avoided. Each of the 125 stroke patients had at least one of the three risk factors.

Starting in 1976, Rexrode, *et al.*[11] conducted a prospective cohort study of 116,759 American nurses, with the aim of examining the relation between BMI and risk of stroke in women. During 16 years, 866 nurses suffered a stroke; of those, 403 had cerebral infarction and 269 had cerebral hemorrhage. As to the relation with BMI, at 27 kg/m^2 or more the risk of cerebral infarction was significantly high. Meanwhile, no relation was observed between cerebral hemorrhage and BMI. In the study, surveyed patients were limited to nurses, but it seems highly reliable in that more than 100,000 nurses were followed up for 16 years.

In a study[12] at Hisayama Town involving a typical epidemiological survey in Japan, from 1961 through 1996 change over time in risk factors for cerebral infarction was examined. The results showed that frequency of hypertension, the most significant risk factor for stroke, hardly changed for either sex. Meanwhile, the rate of those who take depressors among hypertensives increased during the period, and the mean blood pressure of hypertensives decreased sharply. On the other hand, over time the frequency of obesity and impaired glucose tolerance doubled or tripled, and the frequency of hypercholesterolemia increased sharply, to six to ten times. Though obesity was not analyzed as an independent risk factor, the study concluded that correction of obesity, lipid metabolic disorder and impaired glucose tolerance, as well as hypertension, is an important task for the future.

Difference in Obesity Judgment Criteria

Though this is a known fact, it is given here for reference: BMI (kg/m^2) = body weight (kg) ÷ (height (m) × height (m)). In the United States, 25 kg/m^2 is defined as the standard and 30 kg/m^2 and upward is defined as obesity, but in Japan 22 kg/m^2 is defined as the standard (Japan Society for the Study of Obesity; 1999), and obesity is defined as beginning from BMI: 25 (Table 1). In short, while in Western countries obesity is considered normal, in Asia slimness is normal. Since even the definition of obesity is quite different, interpretation of the literature, etc. requires caution. However, since it is known that Japanese more frequently suffer from complications even when their obesity is more modest than that of Western people, and since Asian people are said to be less resistant to obesity than

Table 1 Obesity Criteria

JASSO (1999)	BMI	WHO (1998)
Underweight	<18.5	Underweight
Normal range	18.5≦ ~ <25	Normal range
Obese class 1	25≦ ~ <30	Preobese
Obese class 2	30≦ ~ <35	Obese class I
Obese class 3	35≦ ~ <40	Obese class II
Obese class 4	40≦	Obese class III

JASSO: Japan Society for the Study of Obesity.

Western people, comparison in terms of BMI alone will not be useful. Body fat performs the function of energy storage, and the body fat of an ordinary person accounts for some 18% of body weight. If body fat goes above 25% in a male and above 30% in a female, that person is generally considered obese. While there are various methods of measuring stored body fat, no present methods can be called perfect in terms of price, difficulty, precision, etc. Accordingly, in 1998, when the WHO and the International Association for the Study of Obesity adopted obesity determination using BMI, one of physical constitution indexes, it was a turning point; the Japan Society for the Study of Obesity then also adopted the method (Table 1).

Fat Sleep Apnea Syndrome and Cerebrovascular Disease

Snoring, obstructive sleep apnea (OSA), daytime sleepiness and obesity are recently attracting attention as risk factors for cerebrovascular disease.

Palomaki[13] conducted a case-control study using 177 male cerebral infarction patients and age-matched controls. As a result, he reported that snoring as well as hypertension, ischemic heart disease and excessive alcohol consumption (300 g/week or more) was a significant risk factor for ischemic cerebrovascular disease, and that OSA due to obesity would be the cause.

Shepard[14] also reported that in habitually snoring men the risks of ischemic heart disease, stroke and sudden death during sleep were heightened.

Neau, *et al.*[15] conducted a case-control study of the relation between habitual snoring and cerebral infarction in 133 patients and 133 age- and sex-matched healthy persons. Results showed that the rate of habitually snoring persons was 23.3% for the cerebral infarction group and 8.3% for the control group, a significant difference ($p < 0.001$). In invariably snoring aged male hypertensives, the risk of cerebral infarction was especially high. As a result, the researchers maintained that in treating aged male hypertensives it was important always to inquire about habitual snoring, so as to prevent the onset of cerebral infarction.

Pressman, *et al.*[16] reported two cases in which OSA was the cause of transient ischemic attack (TIA). In both cases, symptoms abated with continuous nasal positive airway pressure. The relation between sleep apnea and cerebrovascular disease has been shown not only in statistical surveys but in real cases as well. Also, they emphasized that in TIA cases caused by OSA, early diagnosis and specific remedies were important for preventing recurrence.

Rangemark, *et al.*[17] compared platelet function and fibrinolytic activity between 13 OSA cases and 10 sex- and weight-matched controls. Results showed that plasminogen activator inhibitor type 1 (PAI-1) value was 18.4 ± 3.6 IU/ml in OSA cases and 8.2 ± 1.7 IU/ml in controls, a significant difference ($p < 0.029$). This result suggested decreased fibrinolytic activity in OSA cases. Although in this study the number of cases was small, the data are notable in showing the mechanism of myocardial and cerebral infarction increase in OSA cases.

Abnormal Body Fat Distribution (Visceral Obesity) and Cerebrovascular Disease

In recent years, body fat distribution has become a subject of discussion; abdominal fat in particular is indicated as becoming a risk factor for cardiovascular disease. Abdominal obesity is expressed by waist-to-hip circumference ratio (WHR) (waist size at navel ÷ maximum hip size). Abdominal obesity is similar to visceral fat obesity. This type of obesity exhibits in many cases multi-risk syndrome, which has been referred to as syndrome X, deadly quartet, etc., accompanied by hypertension, diabetes and hyperlipidemia, based on insulin resistance.

For 18.5 years, Welin, *et al.*[18] conducted a follow-up survey of 789 54-year-old males; 57 (7.2%) of them suffered stroke. Those researchers reported that hypertension, waist size (abdominal obesity), WHR, high serum fibrinogen level, low lung capacity and maternal stroke were significant risk factors, while BMI, serum cholesterol level, hematocrit, blood glucose level, smoking, ischemic heart disease, left ventricular hypertrophy and paternal stroke were not risk factors.

A two-year follow-up survey of 41,837 white females in Iowa conducted by Folsom, *et al.*[19] showed significantly numerous onsets of hypertension in the high WHR group, high WHR being an independent risk factor even with adjustment for other risk factors. Although there were also significantly numerous onsets of stroke in the high WHR group, high WHR became insignificant after adjustment for other risk factors. On the basis of these results, the researchers presumed that high frequency of stroke onset in abdominal obesity was mainly accompanied by diabetes and hypertension.

Table 2 Abstract Table (Obesity as a risk factor for CVD)

Author	Reference No.	Published Year	Study Design	Result
Tanaka, *et al.*	1	1985	prospective	negative
Wilhelmsen	2	1987	prospective	negative
Boysen, *et al.*	3	1988	prospective	negative
Konuma	4	1994	retrospective	negative
Haapaniemi, *et al.*	5	1997	retrospective	negative
Gillum, *et al.*	6	2001	prospective	partly negative
Hubert, *et al.*	7	1983	prospective	partly positive
Herman, *et al.*	8	1983	retrospective	positive
Abbott, *et al.*	9	1994	prospective	positive
Shinton	10	1997	retrospective	positive
Rexrode, *et al.*	11	1997	prospective	positive
Fujishima	12	1999	prospective	probably positive
Palomaki	13	1991	retrospective	probably positive
Shepard	14	1992	retrospective	probably positive
Neau, *et al.*	15	1995	retrospective	probably positive
Pressman, *et al.*	16	1995	case report	probably positive
Rangemark, *et al.*	17	1995	in vitro	probably positive
Welin, *et al.*	18	1987	prospective	partly positive
Folsom, *et al.*	19	1990	prospective	partly positive
Walker, *et al.*	20	1996	prospective	partly positive
Bogousslavsky, *et al.*	21	1985	retrospective	positive
Salonen, *et al.*	22	1988	retrospective	negative
Handa, *et al.*	23	1990	retrospective	negative
Nagatsuka	24	1995	retrospective	negative

However, as a result of examining the correlation between BMI and WHR, they reported that WHR or abdominal obesity was more closely related to stroke onset than was BMI or general obesity.

Walker, *et al.*[20] conducted a follow-up survey of 28,643 health care professionals in the United States with regard to BMI, WHR and the stroke onset rate, to determine whether abdominal obesity was a risk factor for stroke, while recognizing that there was little evidence to confirm that general obesity was a risk factor for stroke. During a 5-year survey period, 118 persons suffered stroke, 80 of whom suffered cerebral infarction. While BMI was not a risk factor, high WHR value was a significant risk factor. However, waist size in itself was not a significant risk factor.

Obesity and Carotid Lesions

Since any carotid lesion is, as a matter of course, a risk factor for cerebral infarction, the relation between obesity and carotid lesion is the relation between obesity and cerebrovascular disease.

Bogousslavsky, *et al.*[21] conducted a case-control study of 159 patients with internal carotid artery stenosis and occlusion as diagnosed by angiography; as risk factors they listed smoking, family history of stroke, ischemic ECG change, obesity, hypertension and hyperglycemia.

Salonen, *et al.*[22] conducted ultrasonic carotid examination of 412 healthy male inhabitants of eastern Finland, and observed arteriosclerotic carotid lesions in 49% of them. As risk factors, they listed high LDL cholesterol value and low HDL cholesterol value, but obesity was not listed.

Handa, *et al.*[23] conducted ultrasonic carotid examination of 232 patients and quantitatively evaluated them by scoring arteriosclerotic lesions. As a result, they listed advanced age, male gender, hyperlipidemia and diabetes as risk factors, but hypertension and obesity were not listed.

Nagatsuka[24] analyzed the results of routine ultrasonic cervical examinations conducted in a physiological function test room on 383 persons from 50 to 80 years of age. Results showed that 66.9% of them had cerebrovascular disease, and hypertension, diabetes and hyperlipidemia were observed in 57.0%, 21.6% and 48.1% of them, respectively. However, no significant relation was observed between obesity and carotid arteriosclerosis.

As indicated above, regarding the relation between obesity and carotid lesions, negative opinions seem to predominate thus far.

Conclusion

Most epidemiological surveys on the relationship between simple obesity and cerebrovascular disease deny any relationship. That is, obesity alone, determined only on the basis of height and weight as shown by BMI, etc., cannot be an independent risk factor for cerebrovascular disease; obesity can become a risk factor only when accompanied by hypertension, hyperlipidemia, impaired glucose tolerance, etc (Table 2). Recently, however, most papers conclude that abdominal obesity is a risk factor for cerebral infarction, provided that there are no data confirming that obesity is a risk factor for hemorrhagic cerebrovascular disease (cerebral hemorrhage and subarachnoid hemorrhage).

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