Relationship between Body Mass Index and Coronary Atherosclerosis Analyzed by Multivessel Angioscopic Study

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Purpose: Low body mass index (BMI) is strongly associated with an increased long-term risk of cardiovascular events. However, there is no evidence of relationship between BMI and the degree of coronary atherosclerosis, and we evaluated the relationship using multivessel angioscopic observation.

Methods: A total of 89 patients with coronary artery disease who underwent angioscopic examination were analyzed. The patients were divided into four categories according to BMI levels: underweight: $<20 \text{ kg/m}^2$ ($n = 7$); normal weight: $20 \text{ to } <25 \text{ kg/m}^2$ ($n = 40$); overweight: $25 \text{ to } <28 \text{ kg/m}^2$ ($n = 27$); and obese: $>28 \text{ kg/m}^2$ ($n = 15$). The number of yellow plaques (NYP) through the observed coronary artery was counted and the color of each plaque was defined as grade 1 (light yellow), grade 2 (yellow), or grade 3 (intense yellow). The NYP per vessel and the maximum yellow grade (MYG) were compared between the four different groups of BMI.

Results: The severity of coronary atherosclerosis was significantly different: NYP per vessel (2.10 ± 1.16 vs. 1.53 ± 0.91 vs. 1.33 ± 0.79 vs. 1.10 ± 0.93 , $p = 0.024$) and MYG (2.57 ± 0.54 vs. 2.25 ± 0.87 vs. 1.96 ± 0.90 vs. 1.93 ± 1.03 , $p = 0.046$). Multivariate regression analysis showed that BMI ($p = 0.024$) independently correlate with the NYP per vessel.

Conclusions: Coronary atherosclerosis in underweight patients was more advanced than normal and overweight patients. Low BMI was independently related to progressive coronary atherosclerosis and that might be a characteristic of vulnerable patients.

Key words: body mass index, coronary artery disease, yellow plaque, obesity paradox

Introduction

Body mass index (BMI) is a common index used for obesity in both clinical practice and epidemiological studies,¹⁾ and several studies have reported an inverse association between BMI and mortality in subjects with coronary artery disease (CAD), so-called the “obesity paradox.”^{2,3)}

A meta-analysis of 40 studies showed that low BMI is strongly associated with an increased long-term risk of cardiovascular events; therefore, we hypothesized that low BMI may be a risk

of coronary atherosclerosis. Coronary angioscopy is a robust imaging modality for assessment of atherosclerotic plaques in vivo.^{4–10)} Angioscopic yellow plaques are commonly observed at the culprit lesion in acute coronary syndrome (ACS),^{4–6)} and they are considered to be vulnerable.¹¹⁾ In addition, the existence of multiple ($n \geq 2$) yellow plaques in the single coronary trunk is regarded as a strong risk factor of future ACS events.¹²⁾ The aim of this study was to investigate the obesity paradox by multivessel angioscopic analysis.

Methods

Patient population

Our institution has a database of angioscopic analysis at the beginning of introducing this technology. Using this system, we

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(Received 2016 03.05; Accepted 2016.08.19)

doi.org/10.15791/angioscopy.0a.16.0010

enrolled all 89 CAD patients who underwent multivessel angioscopic observation between September 2000 and July 2007. ACS was defined as the occurrence of ischemic chest discomfort at rest with electrocardiography (ECG) changes specific to myocardial ischemia, regional wall motion abnormalities by echocardiography, or a previous history of CAD. Patients with elevated cardiac troponin T levels (>0.01 ng/ml) on admission or in the samples taken at 6–8 h after admission were diagnosed with acute myocardial infarction. No elevation of cardiac troponin T is diagnosed as unstable angina. Other patients were defined as stable CAD. Hypercholesterolemia was defined as receiving medication of hypercholesterolemia, fasting serum low-density lipoprotein cholesterol (LDL-C) ≥ 140 mg/dl, or fasting serum total cholesterol ≥ 220 mg/dl. CAD risk factor was defined as hypertension, hypercholesterolemia, diabetes, and smoking. The clinical and laboratory data were collected on the basis of the patients' charts. BMI is defined as the body weight divided by length in meters squared.

The patients were divided into four different BMI categories: <20 kg/m² (underweight); 20 to <25 kg/m² (normal weight); 25 to <28 kg/m² (overweight); ≥ 28 kg/m² (obese), according to previous systematic review of cohort studies indicating the association of BMI and cardiovascular events.²⁾

Angioscopic imaging and analysis

The coronary angioscopic procedure has been reported previously.^{4–10)} Coronary arteries with proximal tortuosity, sharp angle, calcification, or ostial stenosis were not performed because of the expected difficulty in acquiring angioscopic images for the entire vessel. Before observation, the white balance was adjusted for color correction. The light power was adjusted to avoid reflection and to obtain images with adequate brightness for determination of the plaque color. During angioscopic observations, an assistant adjusted the light power to maintain a constant brightness level on the target plaque. Angioscopic images and fluoroscopy during the angioscopic observations were recorded simultaneously on digital videotape for later analysis. The total number of yellow plaques (NYP) was counted for each vessel. The yellow grade was classified semi-quantitatively according to the surface color as 0, white; 1, light yellow; 2, yellow; and 3, intense yellow. The maximum yellow grade (MYG) was defined as the highest yellow grade in all the coronary arteries for each patient. A ruptured plaque was considered to be a wall irregularity, including a tear, flap, or ulceration on the plaque surface. A thrombus was defined as a coalescent red superficial or protruding mass adhering to the vessel surface, but clearly a separate structure that remained after flushing with Ringer's lactate. The angioscopic images

were evaluated by an investigator who was blinded to patients' clinical characteristics. In the previous study performed in our institution, the intra- and inter-observer agreements for evaluated angioscopic items (thrombus, yellow plaque, and complex plaque) were 95%, 100%, and 95%, respectively, and 95%, 98%, and 93%, respectively. The κ values for the intra- and inter-observer agreement of those items were 0.93, 1.00, and 0.88, respectively, and 0.93, 0.95, and 0.84, respectively.⁶⁾

The medical ethics committee at Nippon Medical School Chiba Hokusoh Hospital approved this study protocol (no. 482), and written informed consent was obtained from all the patients before the catheterization procedures.

Statistical analysis

Continuous quantitative data were presented as mean value $\pm$ standard deviation (SD). Comparisons between the four groups were done using analysis of variance (ANOVA) and the least significant difference statistical method. The Jonckheere–Terpstra trend test was used to test for ordered differences in the NYP per vessel and the MYG among the four groups. Categorical variables presented as frequencies were done with Pearson's chi-square test and the Holm method.

Simple linear regression analysis was applied to study the relationship between BMI and NYP per vessel, and multivariate regression analysis was done adjusting for confounding factors (i.e., age and gender) and coronary risk factors (i.e., prevalence of hypertension, smoking status, serum LDL-C, serum hemoglobin A1c (HbA1c), and incidence of ACS). All differences were evaluated at the 95% level of significance ($p < 0.05$). All statistical analyses were performed using IBM SPSS software version 21 (IBM Japan, Tokyo, Japan).

Results

Patients' characteristics

The baseline clinical characteristics are summarized in Table 1. Seven patients (8%) were classified into underweight, 40 patients (45%) into normal weight, 27 patients (30%) into overweight, and 15 patients (17%) into obese. Coronary risk factors including the frequencies of diabetes, hypercholesterolemia, hypertension, smoking status, and the other clinical presentations did not differ among the four groups, excepting for age and BMI levels. Age was higher in patients with underweight, normal weight, and over weight than obese (underweight vs. obese; $p < 0.01$, normal weight vs. obese; $p < 0.001$, over weight vs. obese; $p < 0.05$).

Angioscopic findings

The angioscopic findings are shown in Table 2. The distribution

Table 1. Patients' characteristics

Patients, n	Underweight 7	Normal weight 40	Overweight 27	Obese 15	p Value
Age, years	65.4 ± 8.1	64.1 ± 10.5	59.3 ± 8.6	52.3 ± 12.6	0.002
Gender, male	5 (71%)	29 (73%)	24 (89%)	13 (87%)	0.33
CAD risk factor					
Hypertension	6 (86%)	21 (53%)	18 (67%)	12 (80%)	0.14
Hypercholesterolemia	5 (71%)	37 (93%)	24 (89%)	14 (93%)	0.37
Diabetes	2 (29%)	12 (30%)	7 (26%)	6 (40%)	0.82
Smoking	3 (43%)	16 (40%)	7 (26%)	9 (60%)	0.19
Number of CAD risk factor					
0	0 (0%)	0 (0%)	0 (0%)	1 (7%)	0.307
1	2 (29%)	8 (20%)	8 (30%)	1 (7%)	
2	4 (57%)	19 (48%)	12 (44%)	4 (26%)	
3	1 (14%)	10 (25%)	5 (19%)	6 (40%)	
4	0 (0%)	3 (7%)	2 (7%)	3 (20%)	
Average number of CAD risk factor	1.9 ± 0.7	2.2 ± 0.9	2.0 ± 0.9	2.6 ± 1.1	0.196
BMI (kg/m ²)	18.7 ± 0.6	22.7 ± 1.4	26.1 ± 0.8	30.0 ± 2.1	<0.001
Clinical presentation					
Acute coronary syndrome	3 (43%)	16 (40%)	7 (26%)	7 (47%)	0.517
Acute MI	3 (43%)	11 (40%)	4 (26%)	4 (47%)	0.414
UA	0 (0%)	5 (53%)	3 (74%)	3 (33%)	0.607
Stable CAD	4 (57%)	24 (60%)	20 (74%)	8 (53%)	
Medication					
Statin	4 (57%)	23 (58%)	17 (63%)	9 (60%)	0.93
ACE-I	2 (29%)	11 (28%)	3 (11%)	3 (20%)	0.46
ARB	2 (29%)	14 (35%)	11 (41%)	7 (47%)	0.78
Beta blockers	3 (43%)	9 (23%)	9 (33%)	8 (53%)	0.16
Calcium channel blocker	2 (29%)	11 (28%)	12 (44%)	8 (53%)	0.22
Dual-antiplatelet therapy	6 (86%)	28 (70%)	18 (67%)	11 (73%)	0.84
Laboratory data					
Total cholesterol (mg/dl)	200.1 ± 35.7	197.2 ± 33.8	197.2 ± 36.5	197.0 ± 31.3	0.997
LDL-C (mg/dl)	132.1 ± 34.7	121.7 ± 33.6	125.6 ± 37.4	113.3 ± 35.9	0.623
HDL-C (mg/dl)	43.6 ± 9.8	49.6 ± 16.7	45.0 ± 8.6	42.9 ± 10.2	0.276
LDL/HDL ratio	3.15 ± 1.04	2.67 ± 1.21	2.91 ± 1.16	2.76 ± 1.07	0.708
Triglyceride (mg/dl)	120.7 ± 38.5	137.7 ± 78.8	133.0 ± 52.2	166.6 ± 78.7	0.387
CRP (mg/dl)	0.33 ± 0.30	0.26 ± 0.46	0.21 ± 0.27	0.46 ± 0.99	0.545
HbA1c (%)	6.0 ± 2.0	5.5 ± 1.0	5.8 ± 1.3	5.9 ± 1.0	0.526

Values are numbers (%) or means ± SD.

CAD: coronary artery disease, BMI: body mass index, MI: myocardial infarction, UA: unstable angina pectoris, ACE-I: angiotensin-converting enzyme inhibitors, ARB: angiotensin receptor blockers, LDL-C: low-density lipoprotein cholesterol, HDL-C: high-density lipoprotein cholesterol, CRP: C-reactive protein, HbA1c: hemoglobin A1c

Table 2. Angioscopic findings

Patients, n	Underweight 7	Normal weight 40	Overweight 27	Obese 15	p Value
Observed vessel					
LAD	5 (71%)	37 (93%)	25 (93%)	15 (100%)	0.142
LCx	4 (57%)	29 (73%)	22 (81%)	9 (60%)	0.385
RCA	6 (86%)	22 (55%)	16 (59%)	12 (80%)	0.198
Total NYP	31	136	84	38	
NYP per patients	4.4	3.4	3.1	2.5	
Yellow grade					
Grade 1	10 (32%)	44 (32%)	37 (44%)	11 (42%)	0.150
Grade 2	12 (39%)	65 (48%)	39 (46%)	19 (44%)	
Grade 3	9 (29%)	27 (20%)	8 (10%)	8 (14%)	
Rupture, n	2 (29%)	9 (23%)	3 (11%)	2 (13%)	0.538
Thrombus, n	4 (57%)	13 (33%)	9 (33%)	6 (40%)	0.624

Values are numbers (%).

LAD: left anterior descending artery, LCx: left circumflex artery, RCA: right coronary artery, NYP: number of yellow plaques

Table 3. Multivariate regression analysis for factors influencing number of yellow plaque per vessel

Variables	β Coefficient	<i>t</i> Ratio	<i>p</i> Value
Clinical characteristics			
Age (per 1-year increment)	0.066	0.570	0.570
Gender (female)	0.230	0.421	0.675
Hypertension	0.160	1.511	0.135
Current smoking	-0.095	-0.955	0.343
Clinical presentation			
ACS	-0.043	-0.427	0.670
BMI (per 0.1-kg/m ² decrement)	-0.256	-2.308	0.024
Laboratory data			
LDL-C (per 1-mg increment)	0.339	3.219	0.002
HbA1c (per 0.1-% increment)	0.319	3.198	0.002

ACS: acute coronary syndrome, BMI: body mass index, LDL-C: low-density lipoprotein, HbA1c: hemoglobin A1c

Fig. 1 Angioscopic comparisons of coronary atherosclerosis. The NYP per vessel (A) and MYG (B) are shown. The graded regression of the BMI categories was associated with the NYP per vessel ($p = 0.024$ for trend) and MYG ($p = 0.046$ for trend). NYP: number of yellow plaques, MYG: maximum yellow grade, BMI: body mass index

of the coronary arteries was observed, and the frequency of plaque rupture and thrombus were similar among the four groups. Figure 1 shows the relationship between BMI and angioscopic indexes of yellow plaque. The NYP per vessel and the MYG differed among the four groups (2.10 ± 1.16 vs. 1.53 ± 0.91 vs. 1.33 ± 0.79 vs. 1.10 ± 0.93 , $p = 0.024$, and 2.57 ± 0.54 vs. 2.25 ± 0.87 vs. 1.96 ± 0.90 vs. 1.93 ± 1.03 , $p = 0.046$, respectively).

On simple linear regression analysis, BMI inversely correlated with the NYP per vessel ($R = -0.275$, $p = 0.009$). Multivariate regression analysis showed, taking into account the predefined variables, BMI, serum LDL-C, and HbA1c level to independently correlate with the NYP per vessel (Table 3).

Discussion

This study showed that the NYP per vessel and MYG as angioscopic indexes of coronary atherosclerosis gradually increased according to decreasing in BMI.

Yellow plaque composed of a lipid pool or necrotic core under

a thin fibrous cap is commonly found in the culprit lesion of ACS and that is considered vulnerable plaque.^{4–6,13,14} The yellow grade of the plaque is conversely correlated with fibrous cap thickness, and the thickness of fibrous cap covering of high-grade yellow plaque is extremely less.^{8,15,16} Therefore, it is believed that high-grade yellow plaque is structurally fragile. In addition, angioscopic investigations reported that the patients with the existence of intense yellow plaque or multiple yellow plaques ($n \geq 2$) per vessel is a high risk of suffering from ACS, and those are characteristics of vulnerable patients.^{12,15} Therefore, both NYP per vessel and high MYG indicate not only the severity of coronary atherosclerosis but also patient's vulnerability.

There are many reports showing an inverse correlation between BMI and mortality in patients with CAD.^{3,17–19} Although low BMI is associated with malignancy causing weight loss, the analysis involving 89,056 individuals registered with the Taiwan National Health Insurance showed that increased risk of non-

cancer-related death was associated with low BMI,²⁰⁾ and then low BMI is strongly associated with not only total mortality but also cardiovascular mortality.²⁾ For the first time, this angioscopic investigation directly revealed the association between decreasing BMI and advanced coronary atherosclerosis. However, we cannot clearly explain the relationship between low BMI and advanced coronary atherosclerosis. The several mechanisms of the relationship between BMI and cardiovascular events are considered. Some investigations reported that low lean mass is disadvantage to the incidence of cardiovascular events resulting from a restricted exercise capacity.²¹⁾ Cardiac rehabilitation using physical exercise shows marked reduction of plasma lipid levels and inflammation²²⁾ that might have inhibitory effect of atherosclerosis.

On the other hand, BMI is insufficient to discriminate between fat and lean mass, and unsuitable for estimating those distributions and obesity.²³⁾ In a recent cohort study, low body fat and low lean mass evaluated without BMI invite high mortality of the patients.²⁴⁾ BMI is not a direct index of obesity; our findings therefore may mean not obesity paradox but BMI paradox. Regarding the relationship between BMI and cardiovascular events, prognosis of underweight and severe obesity is poorer than other groups, so-called U-shaped curve is found according to a previous meta-analysis.²⁾ However, subject of our study did not contain patients of severe obesity (BMI ≥ 35 kg/m²). As a result, our study did not show U-shaped curve.

Although BMI paradox in patients with CAD has been established, further researches are needed on the mechanism of BMI paradox. The relationship between lean mass or fatness and coronary atherosclerosis is required to determine the optimal BMI for prevention of CAD.

Conclusions

This study showed that coronary atherosclerosis gradually advanced according to decreasing in BMI. Low BMI was independently related to progressive coronary atherosclerosis and that might be a characteristic of vulnerable patients as well as previous studies.

Study limitations

The present findings were based on observations in a relatively limited number of patients, and excluded any patients who had coronary arteries that were not anatomically suitable for angiography (e.g., ostial stenotic, proximally tortuous, or severely calcified coronary arteries). Therefore, the present data should be considered as exploratory and hypothesis generating. The degree of atherosclerosis evaluated in this study might be higher

than those in general because all patients had already some CAD at baseline.

Acknowledgments

None of the authors have any conflict of interest in relation to the research work described herein. No financial support was received for the study, nor do any of the authors have a relevant relationship with industry.

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