The official journal of the Japan Atherosclerosis Society and
the Asian Pacific Society of Atherosclerosis and Vascular Diseases

Original Article

J Atheroscler Thromb, 2021; 28: 44-51. http://doi.org/10.5551/jat.55145

Current and Past Obesity in Japanese Patients with Critical Limb Ischemia Undergoing Revascularization

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Aim: Recent studies suggested that past history of obesity or maximum body mass index (BMI) in the past was a strong prognostic predictor in a general population. The current study aimed to survey the distribution of current and maximum BMIs and to investigate their prognostic impact in patients with critical limb ischemia (CLI), whose prognosis was poor even after revascularization.

Methods: We analyzed a database of a prospective, multicenter registry in Japan, including 499 CLI patients undergoing revascularization. Their current and maximum BMIs were surveyed at registration. The distribution and the impact on the prognosis were explored.

Results: The estimated means (95% confidence intervals) of current and maximum BMIs were respectively 22.0 (21.7 to 22.3) and 25.3 (24.8 to 25.8) kg/m^2; the difference was 3.3 (2.9 to 3.7) kg/m^2. The prevalence of current obesity (BMI ≥ 25 kg/m^2) was 18% (15% to 22%), whereas 48% (43% to 53%) had ever been obese (maximum BMI ≥ 25 kg/m^2). Past obesity was not rare even in currently lean subjects (BMI < 18.5 kg/m^2), with the prevalence of 18% (7% to 29%). Current BMI, but not maximum BMI, was associated with the mortality risk; the adjusted hazard ratios per 5 kg/m^2 increase were 0.61 [0.46, 0.81] (P=0.001) and 1.07 [0.87, 1.31] (P=0.55), respectively.

Conclusion: The prevalence of current obesity was as low as 18% (15% to 22%) in Japanese CLI patients undergoing revascularization, whereas about a half were formerly obese. Maximum BMI was not independently associated with the mortality risk in the population.

Key words: Critical limb ischemia, Past obesity, Maximum body mass index, Prognosis

Introduction

Obesity is strongly associated with metabolic disorders including diabetes, dyslipidemia, and hypertension and has been well recognized as a risk factor for atherosclerotic cardiovascular diseases[1)]. In this context, it would be no surprise that obesity is common in patients with coronary artery disease (CAD); its prevalence was reported to be around a third in Japan[2)]. On the other hand, clinical studies on critical limb ischemia (CLI), another cardiovascular disease similarly rooted in atherosclerosis, suggested that the prevalence of obesity was much lower[3)]. However, body weight will be changed during a lifetime, and it remained unknown whether the majority of CLI patients had ever been free from obesity. CLI patients have an extremely high prevalence of various comorbidities[4, 5)]; it is of clinical interest whether and how

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Received: January 11, 2020 Accepted for publication: February 9, 2020

these features would be associated with weight history.

Furthermore, recent studies suggest that past obesity or maximum body mass index (BMI) in the past would be a strong prognostic predictor[6-8]. However, no previous studies uncovered whether this would be true of a CLI population, whose prognosis is extremely poor even after revascularization[9-11]. The current study aimed to survey the distribution of current and past BMI and to investigate their prognostic impact in CLI patients undergoing revascularization in Japan.

Methods

We used a clinical database obtained from the Surgical reconstruction versus Peripheral INtervention in pAtients with critical limb isCHemia (SPINACH) study, a prospective, multicenter, observational study that registered patients who had CLI due to atherosclerotic arterial disease in 23 centers (12 vascular surgery departments and 11 interventional cardiology departments) in Japan[9, 12]. CLI patients were registered at the referral to the participating centers, between January 2012 and March 2013. The details of the SPINACH study are described elsewhere[9, 12]. The study was performed in accordance with the Declaration of Helsinki and was approved by the ethics committee at the principal research institution, Asahikawa University Hospital (no. 1023), and all the other centers registering patients. Written informed consent was obtained.

The current analysis included a total of 499 patients in whom major amputation was never performed and revascularization was scheduled for ischemic wound with the Wound, Ischemia, and foot Infection (WIfI) classification system[13] Ischemia grade 2/3 or ischemic rest pain with the WIfI Ischemia grade 3. Skin perfusion pressures of 31–40 mmHg and ≤ 30 mmHg were treated as WIfI Ischemia grades 2 and 3, respectively[9]. Surgical reconstruction and endovascular therapy were scheduled in 187 and 312 patients, respectively.

Data on maximum body weight were obtained from medical records and self-report. Current and maximum BMIs were calculated as current and maximum body weight (kg) divided by the square of current height (m), respectively. Data on maximum body weight were available in 380 patients (76%). Current obesity was defined as current BMI ≥ 25 kg/m^2, whereas past obesity was defined as maximum BMI ≥ 25 kg/m^2. Non-ambulatory status was determined when patients require personal assistance with transferring. The controlling nutritional status (CONUT) score, a laboratory assessment tool of nutritional status, was calculated from serum albumin level, total cholesterol level, and total lymphocyte count[14]. Data on the history of intermittent claudication (claudication history) were obtained from medical records and self-report[15].

Statistical Analysis

Data are given as means and standard deviations for continuous variables or as percentages for discrete variables, if not otherwise mentioned. A P value of < 0.05 was considered statistically significant and 95% confidence intervals are reported when appropriate. The inter-group difference was examined by the Welch's t test for continuous variables and the chi-square test for discrete variables. The association of BMI with the mortality risk was analyzed using the Cox proportional hazards model, whereas that with the risk of major amputation, major adverse limb events (a composite of major amputation and major re-intervention), and a composite of major amputation and any re-intervention was analyzed using the Fine and Gray's proportional hazards regression model for subdistribution of competing risks, with adjustment for mortality. We also analyzed a subgroup with tissue loss at baseline, to investigate the association of BMI with the presence of tissue loss during the follow-up period in this subgroup, using the multinomial logistic regression model. In the model, the dependent variable was composed of the following three categories: alive without tissue loss (set as the baseline category), alive with tissue loss, and dead at each specific time point. Cases alive with major amputation were included in those alive with tissue loss. We additionally examined the prognostic impact of the CONUT score, as well as the baseline characteristics associated with past obesity, on these outcomes. Missing data were addressed by the multiple imputations by chained equations method. All statistical analyses were performed using R version 3.6.0 (R Development Core Team, Vienna, Austria).

Results

Background characteristics of the study population are shown in **Table 1**. They were 73 ± 10 years old, and 87% had ischemic tissue loss. The estimated means (95% confidence interval) of current and maximum BMIs were 22.0 (21.7 to 22.3) and 25.3 (24.8 to 25.8) kg/m^2, with the difference equal to 3.3 (2.9 to 3.7) kg/m^2. Current BMI was significantly correlated with the CONUT score (Pearson's correlation coefficient $r = -0.16$, $P < 0.001$), whereas maximum BMI was not ($r = -0.02$, $P = 0.69$). The distributions of the variables are illustrated in **Fig. 1A**. Current BMI was ≥ 25 kg/m^2 in 18% (15 to 22%) and ≥ 30 kg/m^2

Table 1. Characteristics of study population

n	499
Age (years)	73 ± 10
Male sex	68%
Non-ambulatory status	25%
Receiving welfare	9%
Living alone	16%
Staying at nursing home	7%
Smoking history	60%
Current smoking	15%
Diabetes mellitus	74%
Hypertension	87%
Dyslipidemia	71%
Regular dialysis	53%
Heart failure	19%
Coronary artery disease	42%
Cerebrovascular disease	24%
CONUT score	4.0 ± 2.5
Surgical reconstruction	37%
Tissue loss	87%
Claudication history	54%

Data are mean ± standard deviation, or percentage. Data on the CONUT score and claudication history were missing in 37 (7%) and 1 patient (0.2%), respectively.

in 2% (1% to 3%) of the whole study population, whereas 48% (43% to 53%) had past history of obesity (maximum BMI ≥ 25 kg/m^2) and 15% (11 to 18%) had past history of BMI ≥ 30 kg/m^2. Past obesity was not rare even in currently lean subjects; the prevalence was 18% (7% to 29%) in those with current BMI < 18.5 kg/m^2. On the other hand, current BMI was lower than 18.5 kg/m^2 in 6% (2% to 10%) of those with past obesity. Past obesity was similarly prevalent in the subgroup with diabetes mellitus (**Fig. 1B**), those with hypertension (**Fig. 1C**), those with dyslipidemia (**Fig. 1D**), and those with regular dialysis (**Fig. 1E**).

Patients with past obesity had a younger age, a lower prevalence of non-ambulatory status, and a higher prevalence of history of intermittent claudication (**Table 2**). Subsequent multivariate logistic regression analysis revealed that age, non-ambulatory status, and history of intermittent claudication were independently associated with past obesity; the adjusted odds ratios were 0.77 (0.63 to 0.96) (P=0.017) per 10 year increase, 0.55 (0.34 to 0.89) (P=0.016) and 1.48 (1.00 to 2.20, P=0.049), respectively. Age was also significantly associated with current obesity (74 [73 to 75] years in patients with current obesity versus 70 [68 to 73] years in those without current obesity; P= 0.004). On the other hand, the prevalence of non-ambulatory status was not different between those with and without current obesity (25% [21% to 29%] versus 25% [16% to 34%]; P=0.92). Neither was that of the history of intermittent claudication (54% [49% to 59%] versus 54% [44% to 64%]; P=0.98).

Table 3 demonstrates the impact of current BMI, maximum BMI, and their difference on respective prognostic outcomes, as well as that of the CONUT score and factors associated with past obesity. Current and maximum BMIs, but not their difference, were associated with the risk of mortality in the crude analysis (**Table 3**). Bivariate Cox proportional hazards regression analysis including current and maximum BMIs confirmed that current BMI, but not maximum BMI, was independently associated with the mortality risk; the adjusted hazard ratios per 5 kg/m^2 increase were 0.49 (0.37 to 0.65, P<0.001) and 1.09 (0.89 to 1.33, P=0.41), respectively. Current BMI was still significantly associated with mortality after further adjustment for the CONUT score as well as factors associated with past obesity (**Table 3**). Current and maximum BMIs and their difference were not significantly associated with limb-related outcomes, whereas the CONUT score, as well as age and non-ambulatory status, but not the history of intermittent claudication, was independently associated with mortality and some limb-related outcomes (**Tables 3 and 4**).

Discussion

The current study demonstrated the distribution of current and past BMIs and their prognostic impact in CLI patients undergoing revascularization in Japan.

The prevalence of current obesity in this study was as low as 18% (15% to 22%), which was considerably lower than that reported in previous studies of patients with CAD[2]. These findings support the idea that patient backgrounds would not be identical between a CLI population and a CAD population, although both CLI and CAD are rooted in atherosclerosis[16]. However, the low prevalence of current obesity did not mean that the majority of the CLI population was ever free from obesity. The current study revealed that almost a half had ever been obese. In addition, past obesity was not rare even in currently lean subjects. The CLI population experienced the BMI decrease by 3.3 (2.9 to 3.7) kg/m^2 on average. Obesity accelerates the acquirement of metabolic disorders and increases the risk of atherosclerotic diseases[1], and it is also well known that chronic inflammation, which could be linked to weight loss[17-19], is involved in the progression of atherosclerosis[20]. The commonness of past obesity and subsequent weight loss in this population might reflect these involve-

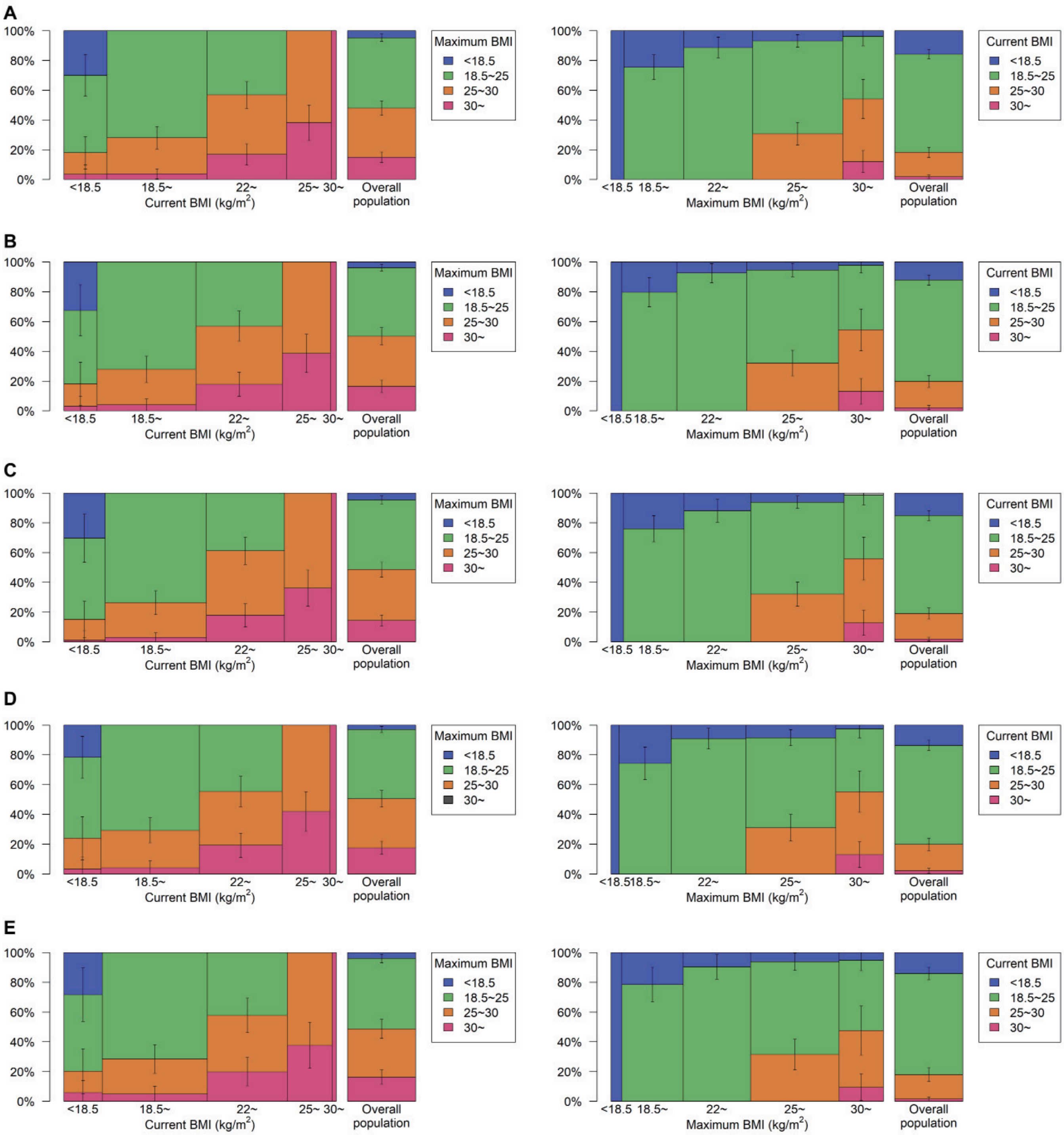

Fig. 1. Distribution of maximum BMI by current BMI (left panel) and that of current BMI by maximum BMI (right panel) in the whole study population (A), the subgroup with diabetes mellitus (B), those with hypertension (C), those with dyslipidemia (D), and those on regular dialysis (E).

The horizontal width of bars indicates the proportion of respective categories of current (left panel) and maximum BMI (right panel). Error bars represent 95% confidence intervals. The mean current and maximum BMIs in each subgroup were estimated to be 22.3 (22.0 to 22.7) and 25.5 (25.0 to 26.1) kg/m^2 in those with diabetes mellitus, 22.1 (21.7 to 22.4) and 25.3 (24.8 to 25.8) kg/m^2 in those with hypertension, 22.2 (21.9 to 22.6) and 25.7 (25.2 to 26.3) kg/m^2 in those with dyslipidemia, and 22.0 (21.6 to 22.4) and 25.4 (24.8 to 26.0) kg/m^2 in those with regular dialysis, respectively

Table 2. Comparison between patients with and without past obesity

	Maximum BMI ≥ 25 kg/m²	Maximum BMI < 25 kg/m²	*P* value
Age (years)	72 [71 to 73]	75 [74 to 76]	0.002
Male sex	66% [60% to 73%]	69% [63% to 75%]	0.57
Non-ambulatory status	18% [13% to 23%]	31% [26% to 37%]	0.001
Receiving welfare	10% [6% to 14%]	9% [5% to 12%]	0.64
Living alone	14% [9% to 18%]	18% [13% to 23%]	0.19
Staying at nursing home	5% [2% to 8%]	8% [5% to 12%]	0.13
Smoking history	62% [55% to 68%]	58% [52% to 64%]	0.40
Current smoking	15% [10% to 19%]	16% [11% to 21%]	0.71
Diabetes mellitus	77% [72% to 83%]	71% [65% to 77%]	0.13
Hypertension	89% [84% to 93%]	86% [82% to 91%]	0.46
Dyslipidemia	74% [68% to 80%]	67% [61% to 73%]	0.11
Regular dialysis	53% [47% to 60%]	52% [46% to 58%]	0.74
Heart failure	19% [14% to 25%]	18% [13% to 23%]	0.70
Coronary artery disease	40% [33% to 46%]	45% [38% to 51%]	0.29
Cerebrovascular disease	26% [20% to 31%]	22% [17% to 28%]	0.42
CONUT score (points)	4.0 [3.7 to 4.3]	4.0 [3.7 to 4.3]	0.97
Surgical reconstruction	40% [33% to 46%]	35% [29% to 41%]	0.36
Tissue loss	90% [86% to 94%]	84% [79% to 89%]	0.098
Claudication history	60% [53% to 66%]	48% [42% to 55%]	0.021

Data are estimates and 95% confidence intervals.

ments during the developmental course of CLI.

The subsequent analysis showed that younger age, ambulatory status, and the history of intermittent claudication were associated with the past history of obesity. In contrast, the CONUT score, a laboratory nutritional assessment, was not associated with past obesity, whereas the score was significantly correlated with current BMI. The developmental course of CLI might be different between older and non-ambulatory CLI patients free from claudication history and younger and ambulatory ones with past history of intermittent claudication. Data on the natural course of CLI development were so far quite limited[21], and the association of obesity remained unclear[22]. Future cohort studies will be needed to reveal the involvement of weight history in CLI development.

Another finding of clinical interest in the current study was the lack of an independent prognostic impact of maximum BMI. Previous studies reported that past obesity or maximum BMI was a strong prognostic predictor[6-8], which was in contrast to the current findings. Furthermore, those studies showed a positive association between maximum BMI and mortality risk, whereas maximum BMI was rather inversely associated with the mortality risk in the crude analysis in the current study. Although the true reasons remained unknown, past obesity and maximum BMI would have a different meaning between a general population and CLI patients. The current finding suggests that maximum BMI would not be a useful marker to predict life and limb prognosis in the population.

The association of current BMI with the mortality risk might be partially explained by the involvement of malnutrition[23]. However, current BMI was associated with the mortality risk independently of the CONUT score, whereas the CONUT score, but not current BMI, had a significant association with limb-related prognosis. BMI might reflect some different aspects of systemic conditions than laboratory nutritional assessments[24].

The current study had some limitations. First, the maximum BMI, derived from maximum body weight, was based on self-report as well as medical records. So was the history of intermittent claudication. Recall of the history might be at risk of inaccuracy. In addition, since the data on height when body weight reached the maximum were unavailable, height at baseline was substituted to calculate the maximum BMI. Second, the SPINACH study did not collect the information on when body weight reached the maximum. Third, neither were detailed data available on the date of wound healing. Therefore, we were unable to assess the impact of BMI on the wound healing rate. Alternatively, we tentatively performed the multinomial logistic regression model to demonstrate the

Table 3. Association with prognostic outcomes

	Crude hazard ratio (Univariate model)	Adjusted hazard ratio (Multivariate model)
Mortality		
Maximum BMI (per 5 kg/m^2)	0.77 [0.66, 0.90] (P=0.001)	1.07 [0.87, 1.31] (P=0.55)
Current BMI (per 5 kg/m^2)	0.53 [0.43, 0.65] (P<0.001)	0.61 [0.46, 0.81] (P=0.001)
Difference (per 5 kg/m^2)	1.13 [0.92, 1.38] (P=0.23)	N/I
CONUT score (per 2 points)	1.37 [1.23, 1.51] (P<0.001)	1.26 [1.13, 1.41] (P<0.001)
Age (per 10 years)	1.42 [1.23, 1.64] (P<0.001)	1.31 [1.12, 1.53] (P=0.001)
Non-ambulatory status	2.80 [2.12, 3.71] (P<0.001)	1.97 [1.45, 2.66] (P<0.001)
Claudication history	1.01 [0.77, 1.32] (P=0.95)	N/I
Major amputation		
Maximum BMI (per 5 kg/m^2)	1.16 [0.81, 1.65] (P=0.43)	N/I
Current BMI (per 5 kg/m^2)	0.92 [0.60, 1.40] (P=0.68)	N/I
Difference (per 5 kg/m^2)	1.39 [0.86, 2.22] (P=0.18)	N/I
CONUT score (per 2 points)	1.44 [1.14, 1.83] (P=0.002)	1.33 [1.04, 1.70] (P=0.021)
Age (per 10 years)	0.70 [0.53, 0.92] (P=0.012)	0.63 [0.46, 0.86] (P=0.003)
Non-ambulatory status	2.33 [1.27, 4.26] (P=0.006)	2.25 [1.13, 4.51] (P=0.022)
Claudication history	0.54 [0.29, 1.00] (P=0.049)	0.60 [0.32, 1.13] (P=0.12)
Major adverse limb events		
Maximum BMI (per 5 kg/m^2)	1.19 [0.94, 1.49] (P=0.15)	N/I
Current BMI (per 5 kg/m^2)	1.12 [0.85, 1.50] (P=0.42)	N/I
Difference (per 5 kg/m^2)	1.21 [0.87, 1.67] (P=0.26)	N/I
CONUT score (per 2 points)	1.23 [1.03, 1.46] (P=0.022)	1.23 [1.04, 1.46] (P=0.016)
Age (per 10 years)	0.70 [0.57, 0.86] (P=0.001)	0.69 [0.56, 0.85] (P=0.001)
Non-ambulatory status	1.50 [0.95, 2.36] (P=0.084)	N/I
Claudication history	1.26 [0.82, 1.94] (P=0.29)	N/I
Composite of major amputation and any re-intervention		
Maximum BMI (per 5 kg/m^2)	1.00 [0.86, 1.16] (P=0.98)	N/I
Current BMI (per 5 kg/m^2)	1.03 [0.86, 1.23] (P=0.77)	N/I
Difference (per 5 kg/m^2)	0.97 [0.79, 1.20] (P=0.81)	N/I
CONUT score (per 2 points)	1.08 [0.97, 1.19] (P=0.17)	N/I
Age (per 10 years)	0.87 [0.77, 0.99] (P=0.040)	0.87 [0.77, 0.99] (P=0.040)
Non-ambulatory status	1.20 [0.89, 1.63] (P=0.23)	N/I
Claudication history	1.04 [0.80, 1.36] (P=0.77)	N/I

Data are hazard ratios [95% confidence intervals] (P values) for mortality, major amputation, major adverse limb events, and a composite of major amputation and any re-intervention. Adjusted hazard ratios were derived from the multivariate model in which variables with significance in the crude hazard ratio (univariate model) were entered. Difference means maximum minus current BMI (i.e., decrease from maximum BMI). N/I, not included.

Table 4. Association with presence of tissue loss during follow-up period in a subgroup with tissue loss at baseline

		At 1 year	At 2 years	At 3 years
Crude relative risk ratio (Univariate model)	Maximum BMI (per 5 kg/m^2)	0.90 [0.66, 1.24] (P=0.52)	1.08 [0.74, 1.60] (P=0.68)	0.86 [0.59, 1.24] (P=0.41)
	Current BMI (per 5 kg/m^2)	0.78 [0.55, 1.11] (P=0.16)	0.82 [0.53, 1.26] (P=0.37)	0.73 [0.49, 1.10] (P=0.13)
	Difference (per 5 kg/m^2)	1.07 [0.71, 1.62] (P=0.74)	1.39 [0.88, 2.19] (P=0.16)	1.04 [0.63, 1.72] (P=0.89)
	CONUT score (per 2 points)	1.27 [1.04, 1.55] (P=0.017)	1.57 [1.19, 2.06] (P=0.002)	1.58 [1.15, 2.19] (P=0.006)
	Age (per 10 years)	0.89 [0.68, 1.17] (P=0.40)	0.82 [0.60, 1.10] (P=0.18)	0.74 [0.53, 1.03] (P=0.073)
	Non-ambulatory status	2.78 [1.56, 4.95] (P=0.001)	3.86 [1.77, 8.43] (P=0.001)	6.12 [2.58, 14.53] (P<0.001)
	Claudication history	0.62 [0.37, 1.05] (P=0.078)	0.74 [0.41, 1.33] (P=0.31)	0.78 [0.42, 1.44] (P=0.42)
Adjusted relative risk ratio (Multivariate model)	CONUT score (per 2 points)	1.20 [0.98, 1.48] (P=0.076)	1.49 [1.13, 1.98] (P=0.006)	1.49 [1.06, 2.09] (P=0.024)
	Non-ambulatory status	2.51 [1.39, 4.55] (P=0.002)	3.21 [1.46, 7.05] (P=0.004)	5.18 [2.13, 12.59] (P<0.001)

Data are relative risk ratios [95% confidence intervals] (P values) for the presence of tissue loss at specific time points. Adjusted relative risk ratios were derived from the multivariate model in which variables with significance in the crude relative risk ratio (univariate model) were entered. Difference means maximum minus current BMI (i.e., decrease from maximum BMI).

association of BMI with the presence of wound (including both unhealed wounds and newly developed wounds) at specific time points. Fourth, the current study population was composed of Japanese CLI patients. In general, obesity is not so prevalent in Japan as in Europe or North America. Whether the current findings would be true in other countries remained unknown.

Conclusion

The current study demonstrated that the prevalence of current obesity was low in Japanese CLI patients undergoing revascularization, whereas almost a half of the patients had ever been obese. Past obesity was not rare even in currently lean subjects. Current BMI, but not maximum BMI, was associated with the mortality risk.

Acknowledgments and Notice of Grand Support

The SPINACH Study is sponsored by Abbott Vascular Japan Co., Ltd, Boston Scientific Japan K.K., Cook Japan Incorporated, Goodman Co., Ltd, Johnson & Johnson K.K., Kaken Pharmaceutical Co.,Ltd, Kaneka Medix Corporation, Medicon Inc., Medikit Co., Ltd, Medtronic Japan Co., Ltd, Mitsubishi Tanabe Pharma Corporation, MSD K.K., St. Jude Medical Japan Co., Ltd, Taisho Toyama Pharmaceutical Co., Ltd, Terumo Corp., W.L.Gore & Associates, Co., Ltd (in alphabetical order). The funding companies played no role in the design of the study, selection of the enrolled patients, revascularization procedures or equipment, or interpretation of the data.

Declaration of Conflicting Interests

The Authors declare that there is no conflict of interest.

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