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Impact of nutritional assessment and body mass index on cardiovascular outcomes in patients with stable coronary artery disease

Ayako Kunimura [a,b,*], Hideki Ishii [a], Tadayuki Uetani [b], Toshijirou Aoki [a], Kazuhiro Harada [a], Kenshi Hirayama [a], Yosuke Negishi [a], Yohei Shibata [a], Takuya Sumi [a], Kazuhiro Kawashima [a], Yosuke Tatami [a], Toshiki Kawamiya [a], Dai Yamamoto [a], Susumu Suzuki [a], Tetsuya Amano [c], Toyoaki Murohara [a]

[a] Department of Cardiology, Nagoya University Graduate School of Medicine, Nagoya, Japan
[b] Department of Cardiology, Chubu Rosai Hospital, Nagoya, Japan
[c] Department of Cardiology, Aichi-Medical University, Nagoya, Japan

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ABSTRACT

Background: An inverse association between obesity, as defined by body mass index (BMI) and prognosis has been reported in patients with cardiovascular disease ("obesity paradox"). The aim of this study was to investigate whether adding nutritional information to BMI provides better risk assessment in patients undergoing elective percutaneous coronary intervention (PCI).
Method: This study comprised 1004 patients undergoing elective PCI. We calculated each patient's controlling nutritional status (CONUT) score for nutritional screening at baseline. Patients were divided into 4 groups based on CONUT score (low, 0–1 [<75th percentile]; or high, ≥2 [≥75th percentile]) and BMI (normal, 18.5–24.9 kg/m^2; or high, ≥25 kg/m^2). The endpoint was major adverse cardiac events (MACE) defined as cardiac death and/or myocardial infarction.
Results: Low CONUT score + normal BMI, low CONUT score + high BMI, high CONUT score + normal BMI, and high CONUT score + high BMI were determined in 374, 242, 275, and 113 patients, respectively. During a median follow-up of 1779 days, 73 events occurred. High CONUT score + normal BMI showed a 2.72-fold increase in the incidence of MACE (95% CI 1.46–5.08, p = 0.002) compared with low CONUT score + normal BMI after adjusting for confounding factors. On the other hand, no significant difference in the incidence of MACE was observed in the other three groups.
Conclusion: The combination of CONUT score and BMI was a useful predictor of MACE in this population. Using BMI to assess the cardiovascular risk may be misleading unless the nutritional information is considered.

1. Introduction

Overweight and obesity have been shown to be associated with high prevalence of cardiovascular risk factors and cardiovascular disease [1]. However, an inverse association between obesity and prognosis has been frequently reported in patients with coronary artery disease [2], which is referred to as the "obesity paradox". Body mass index (BMI) has often been used to define overweightness and obesity in many previous studies. However, there have been criticisms that BMI is insufficient to describe patients' characteristics [3–5].

Previous clinical studies also have demonstrated that underweight patients have the highest incidence of cardiovascular mortality compared with normal-weight and obese patients after percutaneous coronary intervention (PCI) [6]. This association has been referred to as reverse causation, as patients are often likely to be underweight because of an advanced systemic disease, which often cause malnutrition or cachexia. Moreover, most previous studies failed to exclude the influence of non-purposeful weight loss at study enrolment. Malnutrition has been identified as an independent predictor of an unfavourable prognosis in various patient groups, including elderly patients [7], those with end-stage renal disease [8], and those with chronic heart failure [9]. Thus nutritional information may be important for risk stratification and for understanding the obesity paradox in patients with coronary artery disease.

Controlling nutritional status (CONUT) score has reported as an easy and efficient screening tool for malnutrition, especially for early detection and continuous control of hospital malnutrition [10]. The CONUT score has been validated in previous studies and is reported to be as useful as other nutritional assessment tools [11–12]. The aim of this study was to investigate whether adding nutritional information assessed by CONUT score to BMI provides better cardiovascular risk assessment in patients with stable angina pectoris (SAP) undergoing elective PCI.

* Corresponding author at: Department of Cardiology, Nagoya University Graduate School of Medicine, 65 Tsurumai-cho, Showa-ku, Nagoya 466-8550, Japan.
E-mail address: akuni1127@med.nagoya-u.ac.jp (A. Kunimura).

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2. Methods

2.1. Study population

This observational study recruited 1089 consecutive patients with SAP who underwent successful elective PCI at Chubu Rosai Hospital, Nagoya, Japan between January 2006 and December 2012. We excluded patients with active inflammatory disease or malignancy (20 patients), BMI <18.5 kg/m^2 (58 patients), or who were lost to follow-up (7 patients). Thus, this study finally included 1004 patients. All patients had symptoms of effort angina, documented myocardial ischemia or both. This study complied with the Declaration of Helsinki. The ethics committee at Chubu Rosai Hospital approved this study, and all patients provided written informed consent.

2.2. CONUT score and BMI

We calculated each patient's CONUT score by addition of albumin, lymphocytes, and cholesterol scores as previously reported [10]. Serum albumin levels, total lymphocyte counts, and total cholesterol levels were measured before the procedure. Each patient's body weight and body height were measured before the procedure in order to calculate body mass index (BMI). Patients were divided into 4 groups according to CONUT score (low, <75th percentile; or high, ≥75th percentile) and BMI (normal, 18.5–24.9 kg/m^2; or high, ≥25 kg/m^2) [13].

2.3. Coronary angiography and PCI

All patients received antiplatelet therapy for at least 24 hours before the procedure. Furthermore, 5,000 to 10,000 IU of heparin was administered before stenting, and an additional bolus of 1,000 to 2,000 IU was given every hour if the procedure lasted for more than an hour. Baseline angiographies were performed using a computerized quantitative analysis system (QCA-CMS System, version 6.0.39.0; MEDIS, Leiden, the Netherlands) with a guide catheter for calibration. The operators in charge who were blinded to each patient's allocated group, decided on which PCI device and technique to use based on the findings of angiography and the conventional intravascular ultrasound. Successful PCI was defined as a final angiographic residual stenosis of <25% by QCA estimate and Thrombolysis in Myocardial Infarction flow grade 3 at the end of procedures, without a major complication (death or myocardial infarction). Dual-antiplatelet therapy was recommended to continue for at least one year, whereas single-antiplatelet therapy was continued indefinitely to prevent thrombosis after stent implantation.

2.4. Clinical follow-up

Clinical follow-up data were obtained from admission and outpatient medical records or by telephone interview. All patient follow-up data were collected by April 30, 2015. The endpoint of this study was major adverse cardiac events (MACE) defined as the composite of cardiac death or non-fatal myocardial infarction. For patients who had multiple cardiac events during the study period, the time until the first event was used in our analysis. Cardiac death was defined as death resulting from an acute myocardial infarction, fatal arrhythmia, or progression of heart failure. Death from an undetermined cause was not counted as cardiac death. Myocardial infarction was defined when there was evidence of myocardial necrosis in a clinical setting consistent with acute myocardial ischemia with detection of an increase and/or decrease in cardiac biomarker values with at least one value above the 99th percentile upper reference limit and with at least one of the following: (1) symptoms of ischemia; (2) new or presumed new significant ST-segmented wave changes or new left bundle branch block; (3) development of pathological Q waves on electrocardiography; (4) imaging evidence of new loss of viable myocardium or new regional wall motion abnormality; or (5) identification of an intracoronary thrombus on angiography or autopsy [14]. These events were assessed by blinded investigators.

2.5. Statistical analyses

Normally and non-normally distributed continuous variables were expressed as mean ± standard deviation and median (interquartile range), respectively. Categorical variables were expressed as number (proportion). We compared normally distributed continuous variables using analysis of variance (ANOVA), and non-normally distributed continuous variables (total lymphocytes, CONUT score, C-reactive protein, triglycerides and brain natriuretic peptide) using the Kruskal–Wallis test. Categorical variables were compared using Fisher's exact test or the chi-squared test. A Cox proportional hazards model was used to estimate the contribution of CONUT score and BMI to the prediction of MACE during the follow-up period. We considered age, male sex, ejection fraction, brain natriuretic peptide, previous history of PCI or coronary artery bypass grafting, and conventional coronary risk factors (current smoker, estimated glomerular filtration rate, diabetes mellitus, hypertension, and dyslipidaemia) as candidate variables for inclusion in multivariate analysis. The performance of our model in the prediction of MACE with or without CONUT score and BMI was evaluated by calculating c-statistics. Improvements in predictive accuracy were determined by calculating the net reclassification improvement and the integrated discrimination improvement. A p value of < 0.05 was considered statistically significant. Calculations were performed by blinded investigators using SPSS version 18.0 (IBM, Armonk, NY, USA) and R 2.13.1 with PredictABEL and pROC packages (R Development Core Team 2011, Vienna, Austria).

3. Results

3.1. Baseline characteristics

Median CONUT score was 1 (inter quartile range, 0–2). Low CONUT score + normal BMI, low CONUT score + high BMI, high CONUT score + normal BMI, and high CONUT score + high BMI were determined in 374, 242, 275, and 113 patients, respectively. Baseline characteristics are shown in Table 1. Significant differences were observed among groups with regard to age, current smoker, estimated glomerular filtration rate, ejection fraction, brain natriuretic peptide, the prevalence of diabetes mellitus, dyslipidaemia, multiple-vessel disease, previous history of PCI or coronary artery bypass grafting, and use of calcium channel blockers, β-blockers, and angiotensin converting enzyme inhibitors or angiotensin-II receptor blockers. High CONUT score + normal BMI was associated with lower systolic blood pressure and decreased low-density lipoprotein cholesterol and triglyceride levels. Lesion and procedure characteristics are shown in Table 2; no significant association was found among groups.

3.2. Clinical outcomes

During a median follow-up of 1779 days, 73 events were documented. Cox univariate analysis revealed that the hazard ratios (HR) for MACE were 1.48 (95% CI 1.37–1.61, $p < 0.001$) for CONUT score as a continuous value and 0.87 (95% confidence interval [CI] 0.80–0.94, $p = 0.001$) for BMI as a continuous value when analyzed separately. After adjusting for age, male sex, and conventional coronary risk factors (current smoker, estimated glomerular filtration rate, diabetes mellitus, hypertension, and dyslipidaemia), Cox multivariate analysis revealed that the HR for MACE were 1.39 (95% CI 1.26–1.53, $p < 0.001$) for CONUT score and 0.91 (95% CI 0.83–1.00, $p = 0.04$) for BMI, respectively.

Sixteen events (4.3%), 10 events (4.1%), 39 events (14.2%), and 8 events (7.1%) were documented in patients with low CONUT score + normal BMI, low CONUT score + high BMI, high CONUT score + normal BMI, and high CONUT score + high BMI, respectively ($p < 0.001$). The incidence of total MACE and cardiac death were significantly increased in high CONUT score + normal BMI group. There was no significant difference in the incidence of non-fatal myocardial infarction among the groups (Table 3). High CONUT score + normal BMI showed a 2.72-fold increase in the incidence of MACE (95% CI 1.46–5.08, $p = 0.002$) compared with low CONUT score + normal BMI after adjusting for confounding risk factors (Table 4). On the other hand, no significant increase in the incidence of MACE was observed for low CONUT score + high BMI or high CONUT score + high BMI compared with low CONUT score + normal BMI. Adding CONUT score to the established risk factors and BMI increased the predictive accuracy of MACE (Table 5).

The relationship between high CONUT score + normal BMI and MACE was consistent in each subgroup, including age of ≤71 years (50th percentile) versus >71 years, estimated glomerular filtration rate ≥60 ml/min/1.73 m^2 versus <60 ml/min/1.73 m^2, presence versus absence of previous history of PCI or coronary artery bypass grafting, and diabetes mellitus versus non-diabetes mellitus (Fig. 1).

4. Discussion

The current study revealed that both CONUT score and BMI as continuous values were independent predictors of MACE when analyzed separately. Increased BMI was associated with lower incidence of MACE, which demonstrates the obesity paradox. However, when we assessed the combined effect of CONUT score and BMI, high CONUT score + normal BMI was the only group shown to be an independent predictor of MACE. To the best of our knowledge, this is the first study to assess the combined effect of nutritional information and BMI on MACE among patients with SAP. The results of this study suggest that

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