Preoperative HDL-C Predicts Later Cardiovascular Events after Abdominal Aortic Aneurysm Surgery

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Purpose: To determine the predictive value of serum lipid levels on the development of later cardiovascular events after abdominal aortic aneurysm (AAA) surgery.

Methods: A total of 101 patients under 70 undergoing an elective AAA surgery were divided into the following two groups: 1) those who developed later cardiovascular events after AAA surgery, including cerebral infarction (n = 4), catheter intervention (PCI) or surgery for coronary artery disease (CAD) (n = 9) and other vascular disease. (CVE group; n = 19); 2) those without later events (NoCVE group: n = 82). Preoperative atherosclerotic risk factors including serum lipid levels were subjected to univariate and multivariate analysis.

Results: The CVE group showed a significantly lower high-density lipoprotein cholesterol (HDL-C) level (32.9 ± 6.6 vs 41.6 ± 12.1 mg/dL; p < 0.001), higher low-density lipoprotein cholesterol (LDL-C) / HDL-C ratio (4.30 ± 1.01 vs 3.24 ± 1.15; p = 0.001), and higher prevalence of mild CAD (without an indication of PCI) (p = 0.029) preoperatively. Cox hazard analysis indicated that preexistent mild CAD (hazard ratio 4.70) and preoperative HDL-C <35 mg/dL (hazard ratio 3.07) were significant predictors for later cardiovascular events after AAA surgery.

Conclusion: Patients at high risk for later cardiovascular events should require a careful follow-up and may also require an aggressive lipid-modifying therapy.

Key words: abdominal aortic aneurysm, dyslipidemia, cardiovascular events

INTRODUCTION

Arteriosclerosis constitutes the principal etiology of abdominal aortic aneurysm (AAA), which is often associated with other arteriosclerotic cardiovascular diseases like coronary artery disease (CAD).1–5) Recently, the importance of appropriate control of dyslipidemia has been emphasized for the primary prevention of atherosclerotic disease.6–8) Medications aiming at altering the concentrations of circulating lipids have an established role in occlusive atherosclerosis and recent reports described the role of high-density lipoprotein cholesterol (HDL-C) levels in predicting the risk of AAA development.9)

Although patients with AAA are at high risk for developing other atherosclerotic cardiovascular disorders, very few reports have described the value of secondary prevention for atherosclerotic disease after AAA surgery, like lipid modifying therapy related to later cardiovascular events.10) We focused on the atherosclerotic risk factors including serum lipid levels like HDL-C and low-density lipoprotein cholesterol (LDL-C) and investigated the relationship between these risk factors and
later cardiovascular events after AAA surgery in this study. The purpose was to determine the predictive value of serum lipid levels, as well as other atherosclerotic risk factors, on the development of later cardiovascular events after AAA surgery.

Patients and Methods

This retrospective study was performed on 101 patients under 70 who underwent an elective repair of non-ruptured AAA between August 1988 and December 2009 in the Division of Cardiovascular Surgery, Aishin Memorial Hospital. The study subjects were limited to those under the age of 70 at surgery to minimize the influence of aging on the cardiovascular events. All patients were Japanese and consisted of 95 male and 6 female patients with a mean age of 63.2 ± 4.8 years (range from 50 to 69 years). Preexistent atherosclerotic risk factors included a history of treatment of hypertension (HTN) in 66 (65.3 %), diabetes mellitus (DM) in 5 (5%), dyslipidemia treated with statins in 16 (15.8 %), and CAD without an indication for percutaneous catheter intervention (PCI) or coronary artery bypass grafting (CABG) in 32 (31.7 %).

The diagnosis of AAA was established by the findings of enhanced computed tomography (CT) in all cases. In principle patients with AAA greater than 50mm in diameter were determined to have an indication for surgery, and received preoperative coronary artery evaluation by traditional coronary angiography (CAG) or coronary CT (CTCAG). A patient was diagnosed as having CAD when CAG or CTCAG demonstrated that the stenosis was equal to or exceeded 50% (≥50%) in at least one major coronary artery or its main branch. The treatment option for the CAD, such as PCI or CABG, was determined by the strategy resembling the Guidelines proposed by American College of Cardiology (ACC) and American Heart Association (AHA) Task Force Report in 1993 and its updated version.11, 12 Patients who had a severe CAD with an indication for PCI or CABG or those with perioperative coronary events were excluded from the study. Patients presenting with CAD without an indication for PCI or CABG were defined as having “mild” CAD in this study. The procedure of AAA repair in this study was a prosthetic aortic replacement with a bifurcated or tube graft in all patients. Patients with mild CAD received perioperative medical treatment with continuous infusion of trinitroglycerin (TNG) at 0.2 to 0.3 μg/kg/min and/or diltiazem (DTZ) at 0.5 to 2.0 μg/kg/min. There were no operative deaths and no patients with inflammatory or infectious aneurysm in this study, and the etiologic source of AAA was considered to be atherosclerosis in all patients.

Follow-up of the patient after discharge has been performed periodically in principle at the outpatient clinic in our institute. Patients who were referred to other hospital or lost to follow-up within 3 months after discharge were not included in this study. Blood pressure at outpatient clinics during the follow-up period was controlled with a target systolic pressure of less than 140 mmHg and diastolic pressure of less than 90 mmHg. Patients with HTN received angiotensin-converting enzyme inhibitors or angiotensin-II receptor blockers concurrently with additional oral calcium-channel blockers as appropriate. The β-blockers were selected in those with CAD unless patients presented with bradycardia, obstructive pulmonary disease, or severe heart failure. There were 79 patients (78%) receiving a treatment of HTN and 10 patients (10%) receiving a treatment of DM postoperatively.

Cardiovascular events during the follow-up period were defined as the occurrence of cerebral infarction, surgery for other vascular disease, the need for PCI or CABG due to CAD, and deaths from unknown causes. According to the cardiovascular events occurrence, the 101 patients investigated in this study were divided into the following two groups: 1) those who developed later cardiovascular events during the follow-up period after AAA surgery (CVE group; n = 19); 2) those who developed no events later (NoCVE group; n = 82). Clinical features including the age and gender, preexistent risk factors, preoperative and postoperative lipid levels were compared between the two groups. The endpoint of this study for evaluating the rate of freedom from cardiovascular events was defined as the time at cardiovascular events occurrence (CVE group) or time at the end of follow-up for a maximum of 10-years (NoCVE group). The cardiovascular events occurred in the CVE group included the occurrence of cerebral infarction (n = 4), the need for PCI or CABG for CAD (n = 9), surgery for other vascular diseases (n = 9), and death from unknown cause (n = 1). In patients with multiple cardiovascular events, the time at the first event was determined as the endpoint of the study. All smokers were requested to stop smoking before AAA surgery.

For the measurement of lipid levels during the study period, blood samples for biochemical examination were in principle collected after an overnight fast, and the serum was separated and analyzed for total cholesterol (TC),
HDL-C, and triglycerides (TG) using automated assay. Low-density lipoprotein cholesterol (LDL-C) levels were calculated by Friedewald formula. The LDL-C levels during the follow-up period were controlled with a target value of at least less than 130 mg/dL using lipid-modifying medications including statins (n = 49) and fibrates (n = 17) on the physician’s preference. The data of postoperative lipid levels of each patient were determined by the optimum value of laboratory data obtained 3 months or later after AAA surgery. The mean follow-up period after discharge until the endpoint of the study was 55.2 ± 44.1 (months). This study was approved by the Hospital Ethics Committee, and all patients received a full explanation of the surgery, related risks, and postoperative treatment strategy by surgeons.

### Statistical analysis

Continuous variables are presented as the mean ± standard deviation (SD) and are compared using the Mann-Whitney U-test. The chi-square test was employed for comparisons of nominal valuables. The rate of freedom from cardiovascular events (CVE-free rate) was analyzed by the Kaplan-Meier method and comparisons between the two groups were performed by the log-rank test. The endpoint of each patient for calculating these curves was the day of cardiovascular events occurring in the CVE group and the last follow-up day in the NoCVE group as described above. A Cox proportional hazard model was applied to determine the effects of valuables on cardiovascular events during the follow-up period. Differences were statistically considered significant at p < 0.05. SPSS (Ver.12.0J) software (SPSS Inc., Chicago, IL) was used for all statistical analysis.

### Results

Overview of the clinical characteristics and atherosclerotic risk factors compared between the CVE and NoCVE group is summarized in the Table 1. In univariate analysis of preoperative factors, there were no significant differences in the age, gender, systolic and diastolic blood pressure, incidence of a history of HTN, DM, and statins treatment between the two groups. The prevalence of mild CAD was significantly higher in the CVE group than in the NoCVE group (odds ratio (OR) 3.03, 95% confidence interval (CI) 1.09 to 8.44; p = 0.029). Regarding preoperative serum lipid levels, patients in the CVE group showed a significantly lower HDL-C level (32.9 ±

| Clinical Factors | TOTAL (n = 101) | CVE(+) (CVE group; n = 19) | CVE(-) (NoCVE group; n = 82) | p value |
|------------------|----------------|---------------------------|-----------------------------|--------|
| Age              | 63.2 ± 4.8     | 62.7 ± 4.3                | 63.4 ± 4.9                  | 0.579  |
| Male/Female      | 95/6           | 18/1                      | 77/5                        | 0.89   |
| HTN treatment (%)| 66 (65.3 %)    | 14 (73.7 %)               | 52 (63.4 %)                 | 0.397  |
| DM treatment (%) | 5 (5.0 %)      | 2 (10.5 %)                | 3 (3.7 %)                   | 0.214  |
| statins (%)      | 16 (15.8 %)    | 5 (26.3 %)                | 11 (13.4 %)                 | 0.165  |
| CAD (%)          | 32 (31.7 %)    | 10 (52.6 %)               | 22 (26.8 %)                 | 0.029  |
| pre SBP (mmHg)   | 125.4 ± 18.5   | 121.8 ± 19.9              | 126.3 ± 18.2                | 0.35   |
| pre DBP (mmHg)   | 70.6 ± 11.7    | 69.7 ± 14.5               | 70.8 ± 11.1                 | 0.732  |
| pre HDL-C (mg/dL)| 40.0 ± 11.7    | 32.9 ± 6.6                | 41.6 ± 12.1                 | <0.001 |
| pre LDL-C (mg/dL)| 127.4 ± 29.1   | 137.5 ± 25.1              | 125.2 ± 29.5                | 0.113  |
| pre LDL-C/HDL-C  | 3.43 ± 1.19    | 4.30 ± 1.01               | 3.24 ± 1.15                 | 0.001  |
| pre TG (mg/dL)   | 139.1 ± 72.6   | 140.9 ± 64.6              | 138.7 ± 74.6                | 0.906  |

CVE, cardiovascular events; OR, Odds Ratio; CI, confidence interval; HTN, hypertension; DM, diabetes mellitus; CAD, coronary artery disease; SBP, systolic blood pressure; DBP, diastolic blood pressure; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TG, triglyceride; pre, preoperative; post, postoperative
6.6 vs 41.6 ± 12.1 mg/dL; p < 0.001), higher LDL-C/HDL-C ratio (4.30 ± 1.01 vs 3.24 ± 1.15; p = 0.001) than those of the NoCVE group. Differences of the serum LDL-C levels and triglyceride levels did not reach statistical significance.

Serum lipid levels during the follow-up period after AAA surgery are also shown in the Table 1 as postoperative values. There were no significant differences in the postoperative HDL-C, LDL-C, and TG levels and LDL-C/HDL-C ratio. The mean follow-up period was 48.8 ± 39.5 (range 4 to 114) months for the CVE group and 57.2 ± 46.1 (range 3 to 120) months for the NoCVE group, which showed no significant difference (p = 0.47). There were 5 deaths in the NoCVE group during the follow-up period, including deaths from lung cancer (n = 2; at 31 and 102 months after surgery), esophageal cancer (n = 1; 87 months after surgery), pneumonia (n = 1; 91 months after surgery), and head injury (n = 1; 6 months after surgery). These cases were represented as censored cases in the calculation of the Kaplan-Meier method and a Cox proportional hazard model. In the CVE group, one patient died from unknown cause as described above.

Since the HDL-C levels were significantly different between the two groups, we compared the cardiovascular event-free (CVE-free) rate between patients with preoperative serum HDL-C levels ≤35 mg/dL (n = 44) and those with HDL-C levels >35 mg/dL (n = 57). The cut-off value (35 mg/dL) was calculated from receiver-operating characteristics curves (ROC curve) using statistical software. Figure 1 shows a comparison of Kaplan-Meier curves indicating the rate of freedom from cardiovascular events between the two patient groups divided based on the preoperative HDL-C levels. As shown in the Figure 1, there was a significant difference in the CVE-free rate depending on the preoperative HDL-C levels. Patients with preoperative HDL-C levels >35 mg/dL had a significantly better CVE-free rate (p = 0.033 by the log-rank test).

Based on the results from univariate analysis and CVE-free rate analysis, clinical factors that may be related to the development of cardiovascular events were assessed with multivariate analysis using Cox proportional hazard model with stepwise method to identify correlations with the later events occurrence. The items assessed included an age, a history of treatment of HTN and DM, presence of preexistent mild CAD, the serum HDL-C levels ≤35 mg/dL, and TG levels as preoperative factors. The results are shown in the Table 2, which indicated that the cardiovascular event occurrence was significant correlated with the presence of a mild CAD (hazard ratio 4.70, p = 0.003) and the serum HDL-C levels ≤35 (mg/dL) (hazard ratio 3.07, p = 0.038) in the preoperative factors.

**Discussion**

AAA is an asymptomatic condition with a high mortality rate related to rupture, which has been the cause of 1% to 2% of all deaths in the Western world. Several studies reported a coexistence of atherosclerosis or disturbed connective tissue metabolism with AAA as an underlying etiology, but the evidence for the role of lipids in the development of an AAA remains to be investigated.

| Table 2  | Relationship between risk factors and cardiovascular events by multivariate analysis using Cox proportional hazard model |
|----------|-------------------------------------------------------------------------------------------------|
| Risk Factors | Hazard Ratio | 95% CI | p value |
| Age      | 0.97 | 0.86–1.09 | 0.561 |
| HTN      | 1.14 | 0.33–3.94 | 0.837 |
| DM       | 1.84 | 0.54–6.27 | 0.329 |
| CAD      | 4.7  | 1.70–12.98 | 0.003 |
| HDL-C <35 | 3.07 | 1.06–8.86 | 0.038 |
| TG       | 1    | 0.99–1.01  | 0.516 |

CI, confidence interval; HTN, hypertension; DM, diabetes mellitus; CAD, coronary artery disease; SBP, systolic blood pressure; DBP, diastolic blood pressure, HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; TG, triglyceride
controversial.\textsuperscript{15–17} Hobbs et al reported the highly significant association between LDL-C and small AAA, and LDL-C could be an initiating factor in the development of an AAA.\textsuperscript{18} A recent report by Golledge et al. indicated that HDL-C appeared to be the most important lipid in predicting the risk of AAA development.\textsuperscript{9} Forsdahl et al. described the association of statin prescription with the development of an AAA in their report from the Tromso study.\textsuperscript{5} These reports mainly described the primary prevention of the development of an AAA, but few reports mentioned the secondary prevention for atherosclerotic disease after AAA surgery.\textsuperscript{10} As AAA represents a progress in systemic atherosclerosis, patients undergoing surgical treatment of AAA should be followed up to prevent other cardiovascular disorders.

In general, increasing age is consistently identified as a strong risk factor for atherosclerotic disease like AAA in the past literature;\textsuperscript{5} thus, the age distribution of the study group may have a significant influence on the results from the study like this investigation. For example, the Tromso study included a very wide range of ages (25 to 82 years); thus, the results may not reflect the true risk factors because the risk period for the development of an AAA did not occur for many patients aged ≤50 years during the study period.\textsuperscript{5} To minimize the influence of aging on the events during the follow-up period, the subjects in this study were limited to those under 70 (range 50 to 69) at surgery.

In the analyses of preoperative factors, the prevalence of mild CAD, the serum HDL-C levels and LDL-C/HDL-C ratio were found to have significant differences between the CVE group and the NoCVE group. The mean preoperative HDL-C level in all patients was as low as 40.0 ± 11.7 mg/dL, and the LDL-C/HDL-C ratio was as high as 3.43 ± 1.19, which were consistent with results from previous reports describing that decrease in the HDL-C levels and increase in the LDL-C/HDL-C ratio enhanced the risk for the development of an AAA.\textsuperscript{3, 15} Our results showing that further decrease in the preoperative HDL-C levels enhanced the risk for cardiovascular events after AAA surgery may be reasonable, and there was about a three-fold higher risk of developing cardiovascular events in those with the preoperative HDL-C levels ≤35 mg/dL. Patients with preexistent mild CAD are likely to have progression of arteriosclerosis in other arteries; thus, our results seem to be consistent with previous findings.\textsuperscript{3, 10}

These results indicate that patients at risk for the development of later cardiovascular events, including those with lowered HDL-C levels <35 mg/dL and those with preexistent CAD, should be carefully followed-up to prevent later cardiovascular events after AAA surgery. In general, LDL-C at a high serum level may accumulate in the artery wall where they are oxidized and taken up by foam cells in a process that leads to the development and progression of atherosclerosis.\textsuperscript{6} HDL-C is reported to oppose atherosclerosis by removing cholesterol from foam cells, by inhibiting the oxidation of LDLs, and by limiting the inflammatory processes that underlie atherosclerosis.\textsuperscript{6} Based on these findings, some reports advocated that LDL-C/HDL-C ratio can be used as a beneficial treatment index although the serum LDL-C levels are mainly employed as a treatment target in previous reports.\textsuperscript{1, 15, 18} Based on our results, HDL-C may play an important role not only in the development of AAA\textsuperscript{9} but also in the development of later cardiovascular events after AAA surgery. Patients in our series generally had a low level of HDL-C, but those with preoperative HDL-C levels ≤35 may have a further higher risk for the development of cardiovascular events after AAA surgery.

There are some limitations in this study. In our study design, patients with AAA were retrospectively divided into the two groups based on the patient outcome as to whether they had cardiovascular events or not later, as a single center experience. Lipid-modifying therapy was not given to all patients after surgery based on the condition of patients. Ideally, a randomized prospective study is required to determine the value of predictor with a larger number of patients. Second, the findings of our study were limited to those aged <70 at surgery; thus, the value of lipid-modifying therapy in patients with age older than the present study group is unknown. Since the majority of subjects were male patients, we can draw no conclusions on the association of lipids with cardiovascular events in women. Third, the follow-up period is relatively short in some patients; thus, the short follow-up period may influence the incidence of cardiovascular events. Although there are many limitations, our study results may help to understand the predictive value of serum lipid levels and to prognosticate the outcome at least in part of patients with AAA.

In conclusion, our study indicated that a decrease in the preoperative HDL-C levels ≤35 mg/dL and the presence of CAD were significant predictors for the development of later cardiovascular events during follow-up after AAA surgery. These patients at high risk for later cardiovascular events should require a careful follow-up and may also require an aggressive lipid-modifying therapy.
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