Abstract
Purpose: Recent studies have reported that glycated albumin (GA) levels have can be used to monitor blood glucose control. Because the half-life of albumin is shorter than that of erythrocytes, serum GA levels better reflect shorter-term glycemic control status than glycated hemoglobin (HbA1c). We measured serum GA levels in patients who underwent surgery and analyzed the relations of such levels to preoperative co-morbidity to examine whether serum GA levels are a useful preoperative risk factor.
Methods: We studied GA levels, preoperative co-morbidity, laboratory findings, and surgical procedures in adults who underwent surgery. Patients were divided into 2 groups according to whether the GA level was \( \geq 16.5\% \) (GAH group) or <16.5% (GAN group).

Results: The study group comprised 1,258 patients. Preoperative co-morbidity of coronary artery disease occurred in 28.4% of the GAH group (n=225) and 6.5% of the GAN group (n=1,033). Preoperative co-morbidity of cerebrovascular disease occurred in 16.0% of the GAH group and 5.1% of the GAN group. There were significantly more of these preoperative co-morbidity \( (p<0.01) \) in the GAH group than in the GAN group.

Conclusions: The measurement of GA levels can facilitate the early detection of diabetes mellitus in surgical patients and can also contribute to the management of perioperative complications.

Key words: glycated albumin level, coronary artery disease, cerebrovascular disease

Introduction
An understanding of preoperative glycemic status is essential because hyperglycemia can negatively affect the perioperative status of patients\(^1\)\(^-\)\(^5\). Glycated hemoglobin (HbA1c) levels have been widely used as an index of preoperative glycemic control, which is important for the risk of vascular disease. Recent studies have reported that glycated albumin levels are an excellent indicator of glycemic control, particularly in patients with anemia, such as those undergoing dialysis and pregnant women, in whom HbA1c levels do not provide an accurate assessment of glycemic control\(^6\)\(^-\)\(^10\).

In contrast to blood glucose levels and HbA1c levels, glycated albumin levels can be easily measured within a short time using serum samples and the same instruments as other blood chemical tests, and the cost is reasonable\(^11\)\(^,\)\(^12\). In Japan, glycated albumin levels are therefore now measured in all blood donors, contributing to the early detection and treatment of diabetes mellitus and potentially reducing healthcare expenses by preventing adult-onset diseases.

During the past 20 years, an increasing number of patients with diabetes mellitus have undergone surgery\(^10\). We have continuously measured preoperative glycated albumin levels in all adult patients who undergo surgery at Tokyo Women's Medical University Medical Center East to analyze whether glycated albumin levels are related to the preoperative co-morbidity of vascular disease due to diabetes and to examine whether such levels can be used to predict risks of the preoperative co-morbidity.

Methods
The approval number of the present protocol by the ethics committee at Tokyo Women's Medical University...
sity was 2,492. During 9 months from June 2012 through March 2013, a total of 2,768 patients under-went surgery at Tokyo Women's Medical University Medical Center East. We excluded patients who un-derwent emergency surgery and patients younger than 20 years and studied 1,258 adults (age, 20 to 93 years; mean age, 60.1 ± 16.2 years) who were sched-uled to undergo surgery under general anesthesia and gave written informed consent to participate in the study.

Glycated albumin levels (normal range, 11% to 16%) were measured by an enzymatic method (Asa-hi Kasei Co., Ltd., Tokyo, Japan), using a liquid chemistry system (GA assay, Asahi Kasei Co., Ltd.)\(^{11,12}\). Blood samples for measurement of glycat-ed albumin levels were collected along with samples for routine preoperative tests. Surgical procedures, disease history, preoperative co-morbidity (coronary artery disease, cerebrovascular disease, and renal failure), and laboratory findings were obtained from anesthetic records.

As an index of atherosclerosis, intima-media thick-ness (IMT) was measured on carotid artery ultraso-nography in 98 patients scheduled to undergo cardio-vascular surgery or brain surgery\(^{14,15}\). An IMT or ≥1.1mm was considered abnormal, strongly sug-gesting the presence of atherosclerosis\(^{15}\).

### Statistical Analysis

The data are reported as means, standard deviations (SD), or numbers of patients (percentage). The study variables were compared between patients with a glycated albumin level of 16.5% or higher (GAH group) and those with a glycated albumin level of less than 16.5% (GAN group). This cut-off level is determined according to the recent study\(^{6}\). Statistical analysis was performed with the chi-square test, unpaired-t test, Mann Whitney–U test, and chi-square for independence test assessing any signifi-cant difference between the two groups. \(p\) values of less than 0.05 were considered to indicate statistical significance.

### Results

Among the 1,258 subjects, 225 patients (17.9%) be-longed to the GAH group, and 1033 (82.1%) belonged to the GAN group. The demographic characteris-tics of the patients (sex, age, height, body weight, and body-mass index) are shown in Table 1. Age differed significantly between the groups (\(p<0.001\)). Table 2 shows the surgical procedures performed in the GAH group and the GAN group. The numbers of patients and percentages are shown. A signifi-cantly high proportion (25.8%) of patients (\(p=0.03\)) underwent cardiovascular surgery in the GAH group, and no significantly high proportion of pa-tients is found in the other surgeries.

As for preoperative co-morbidity, 64 patients (28.4%) in the GAH group (\(n = 225\)) and 67 (6.5%) in the GAN group (\(n = 1033\) ) had coronary artery dis-ease, and 36 (16.0%) in the GAH group and 53 (5.1%) in the GAN group had cerebrovascular disease. The proportions of patients with coronary artery disease (\(p<0.001\)) and cerebrovascular disease (\(p<0.001\)) were significantly higher in the GAH group than in the GAN group (Fig. 1). The average GA levels for the patients with and without cor-onary artery disease and cerebrovascular disease are given in Table 3. They are significantly higher for the patients with these diseases (\(p<0.001\)) than those without them.

Because age differed significantly between the groups (\(p<0.001\)), a subanalysis of patients 60 years or older (age adjustment) was performed to compare the prevalences of coronary artery disease and cerebrovascular disorders between the groups. The mean age was 72.2 ± 7.2 years in the GAH group (\(n=191\)) and 71.4 ± 6.8 years in the GAN group.

<table>
<thead>
<tr>
<th>Table 1 Patient Demographics</th>
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<tr>
<td>Total</td>
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<tr>
<td>Number of patients (M/F)</td>
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<td>Age (years)</td>
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<td>Body mass index (kg/m(^2))</td>
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Data are numbers (male/female) or mean ± SD.

GAH group: glycated albumin level was ≥16.5%.
GAN group: glycated albumin level was <16.5%.
(n=582), with no significant difference between the groups. After age adjustment, 57 patients (29.8%) in the GAH group and 58 (10.0%) in the GAN group had coronary artery disease, and 34 patients (17.8%) in the GAH group and 45 (7.7%) in the GAN group had cerebrovascular disorders. The proportions of patients with coronary artery disease (p<0.001) and cerebrovascular disorders (p<0.001) were significantly higher in the GAH group than in the GAN group among patients 60 years or older (Fig. 1).
The average GA levels for the patients with and without coronary artery disease and cerebrovascular disorders are given in Table 3. They are significantly higher for the patients with these diseases \( (p<0.001) \) than those without them even after age adjustment.

Ten patients \( (4.4\%) \) in the GAH group \( (n=225) \) and 21 \( (2.0\%) \) in the GAN group \( (n=1,033) \) were receiving maintenance dialysis. The prevalence of renal failure was significantly higher in the GAH group than in the GAN group \( (p=0.04) \). After age adjustment, 10 patients \( (5.2\%) \) in the GAH group \( (n=191) \) and 19 \( (3.3\%) \) in the GAN group \( (n=582) \) were receiving maintenance dialysis, with no significant difference between the groups in the prevalence of renal failure \( (p=0.45) \). The average GA levels for the patients with and without renal failure are shown in Table 3. They are significantly higher for the patients with it \( (p<0.05) \) than those without it. After age adjustment, however, there is no significant difference.

The mean IMT on carotid artery ultrasonography in patients who were scheduled to undergo cardiovascular surgery or brain surgery was \( 1.23 \pm 0.41 \) mm in the GAH group and \( 0.95 \pm 0.25 \) mm in the GAN group. The mean IMT was significantly greater in the GAH group \( (p=0.001) \). In the GAH group, 19 \( (61.3\%) \) of 31 patients had an IMT of \( \geq 1.1 \) mm, with a mean age of \( 73.4 \pm 8.6 \) years. In the GAN group, 17 \( (25.4\%) \) of 67 patients had an IMT of \( \geq 1.1 \) mm, with a mean age of \( 71.1 \pm 8.8 \) years. The proportion of patients with an IMT of \( \geq 1.1 \) mm was significantly greater in the GAH group \( (p=0.001) \), indicating that the prevalence of atherosclerosis was significantly higher in the GAH group. As compared with the GAN group, the GAH group had a greater mean IMT and a higher proportion of patients with an IMT of \( \geq 1.1 \) mm. The atherosclerotic index was similar \( (p=0.21) \) in the GAH group \( (2.22 \pm 0.83) \) and the GAN group \( (2.32 \pm 0.86) \).

**Discussion**

The results of the present study suggested that glycated albumin levels are useful for the detection of diabetes mellitus and the prediction of macrovascular disease and atherosclerosis. Although we did not compare glycated albumin levels with HbA1c levels in the present study, previous studies have indicated that glycated albumin levels can predict complications similar to HbA1c levels\(^4,5\). Because HbA1c levels are now widely used as the gold standard of glycemic control, we compared glycated albumin levels with HbA1c levels.

Because hemoglobin has a long lifespan of 120 days, HbA1c levels reflect glycemic status during the past 2 to 3 months\(^6,16,17\). Therefore, HbA1c levels are not an accurate index of glycemic control in patients with pathological conditions associated with rapidly fluctuating blood glucose levels or with anemia or abnormal hemoglobin\(^7-10,18\). Moreover, HbA1c levels closely reflect mean blood glucose levels, but not blood glucose levels after meals. Therefore, HbA1c levels are only weakly related to diabetic complications associated with postprandial blood glucose levels, such as atherosclerosis\(^19\). In contrast, because albumin has a half-life of 16 to 17 days, glycated albumin levels are considered to mainly reflect glycemic status during the past 2 to 3 weeks\(^6,16,17\). The binding rate of albumin to glucose is about 10 times higher than that to hemoglobin, and albumin is rapidly glycated\(^20\). Therefore, glycated albumin levels are considered to be affected by short-term fluctuations in blood glucose levels. Glycated albumin levels thus reflect short-term fluctuations in blood glucose levels.
changes in blood glucose levels, without being affected by abnormal hemoglobin metabolism. Furthermore, glycated albumin levels reflect postprandial blood glucose levels or fluctuations in blood glucose levels in addition to mean blood glucose levels. Because glycated albumin levels more sensitively reflect recent blood glucose levels than do HbA1c levels, glycated albumin levels are thus suitable for monitoring changes in blood glucose levels in situations that require relatively rapid glycemic control, such as in pregnant women and preoperative patients.

In patients with diabetes mellitus, glycated albumin levels strongly correlate with postprandial blood glucose levels. Postprandial hyperglycemia has been shown to be intimately related to the development of macrovascular disease. Pu et al. reported that glycated albumin levels are a predictor of the onset as well as the severity of coronary artery disease, whereas HbA1c levels are not. These findings indicate that glycated albumin levels are a better index of glycemic control than HbA1c levels. Glycated albumin levels may thus become more widely used and replace HbA1c levels as an index of preoperative glycemic control.

In patients undergoing hemodialysis, erythrocyte survival is shortened by factors such as renal anemia, the use of erythropoietin, and dialytic procedures, lowering HbA1c levels as compared with actual glycemic control status. Glycated albumin levels thus more accurately reflect blood glucose levels. Glycated albumin levels have been reported to similarly correlate with blood glucose levels in patients receiving hemodialysis and in those with normal renal function. Recent studies have reported that glycated albumin levels should be used rather than HbA1c levels to more accurately evaluate vascular disease and predict survival in diabetic patients who are receiving dialysis. Okada et al. reported that HbA1c and glycated albumin levels do not accurately predict mortality among diabetic patients with end-stage renal failure who were undergoing dialysis, whereas elevated glycated albumin levels are associated with a significantly higher progression rate of cardiovascular disease. Fukuoka et al. showed that high glycated albumin levels are a significant predictor of mortality, whereas HbA1c levels are not in diabetic patients undergoing dialysis. The results of these studies suggest that glycemic control is a determinant of survival and the risk of cardiovascular disease in diabetic patients who are receiving dialysis. Glycemic management based on glycated albumin levels may thus be therapeutically useful in such patients. In pregnant women with diabetes mellitus, strict glycemic control is required to prevent neonatal as well as maternal complications. Because pregnancy is associated with anemia, glycated albumin levels are considered an accurate index of glycemic control. A target glycated albumin level of less than 15.8% has been recommended.

In our study, we measured IMT as an index of atherosclerosis, and the proportion of patients with atherosclerosis was higher in the GAH group. Glycated albumin levels are thus considered a useful predictor of the risk of atherosclerosis. The underlying reason is that atherosclerosis is associated with large hemodynamic changes during the perioperative period, increasing the risk of the recurrence and exacerbation of cardiovascular events. The perioperative development of such events negatively affects postoperative outcomes. To prevent these events, patients should be closely monitored and their condition carefully managed. The ability of glycated albumin levels to predict the risk of perioperative cardiovascular events that are not significantly related to HbA1c is expected to contribute to the prevention of such events.

As compared with the measurement of HbA1c levels, glycated albumin levels are considered more useful as a preoperative examination because glycated albumin levels more closely reflect short-term changes in blood glucose levels, require smaller amounts of blood samples, can be assessed simultaneously with routine examinations, are more straightforward and less expensive, and are an excellent indicator of glycemic control in patients with conditions such as renal failure or anemia.

Our study had several important limitations. The study group was limited to patients who underwent elective surgery, and carotid artery ultrasonography was performed to evaluate atherosclerosis only in patients who underwent cardiovascular surgery or brain surgery. In addition, long-term outcomes were not analyzed.

**Conclusion**

The proportions of patients with coronary artery
disease ($p<0.01$) and cerebrovascular disease ($p<0.01$) were significantly higher in the GAH group than in the GAN group. Measurement of glycated albumin levels will most likely facilitate the prevention of the exacerbation of the diabetic preoperative co-morbidity, and the management of the complications in patients with diabetes mellitus who are scheduled to undergo surgery.

Acknowledgements
We are greatly indebted to the surgeons from the Department of Surgery for their cooperation in this study.

(This study was partially presented at the annual meeting of the American Society of Anesthesiologists, San Francisco, October 2013 and the 38th Annual Congress of Japanese College of Surgeons, Tokyo, June 2013.)

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