Evaluating the role of serum 1,5-anhydroglucitol concentrations as an indicator of hyperglycemic changes in diabetic and nondiabetic surgical patients

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Abstract (241 words)

Purpose

We investigated the relationship between plasma glucose and serum 1,5-anhydroglucitol (1,5-AG) concentrations in surgical patients to determine the role of 1,5-AG concentrations in perioperative glycemic control.

Methods

We enrolled 57 patients (19 with and 38 without diabetes) in the study, who underwent hepatectomy under general anesthesia with sevoflurane and remifentanil. Plasma glucose and serum 1,5-AG concentrations were measured and their correlations were evaluated.

Results

In all patients, plasma glucose concentrations increased significantly during hepatectomy, but serum 1,5-AG concentrations declined after surgery. Linear regression analysis revealed a weak but significant correlation between the decrease rate of 1,5-AG concentrations and the increase rate of plasma glucose concentrations. Regression analyses revealed this correlation to be more intense in patients without diabetes than in all patients, whereas no correlation was observed in patients with diabetes. These results suggest that serum 1,5-AG concentrations decrease significantly in proportion to increase in plasma glucose concentrations in patients without diabetes, but are less sensitive to such changes in patients with diabetes. Consequently, this indicates that preoperative serum 1,5-AG concentrations in patients with diabetes are too low to be influenced by glycemic fluctuations. In both patient groups, decreased 1,5-AG concentrations did not normalize until 72 h after initiation of surgery.

Conclusion

Measurement of 1,5-AG concentrations may be a useful for evaluating glycemic control during anesthesia in patients with normal glycemic metabolism; however, this approach may not be as useful in patients with diabetes as in those without diabetes.

Introduction

Inadequate treatment of hyperglycemia leads to an increase in the prevalence of morbidity and mortality for various medical conditions as well as for surgical procedures [1–3]. Thus, monitoring glucose fluctuation is important in order to avoid poor metabolic control in surgical patients, even in those who do not have diabetes mellitus (DM).

1,5-Anhydroglucitol (1,5-AG), the 1-deoxy form of glucose, is structurally similar to glucose and has been suggested to be a novel marker of carbohydrate metabolism in patients with DM [4–5]. Serum 1,5-AG concentrations fluctuate in response to changes in blood glucose concentrations. This offers more timely information regarding glycemic control than other indicators of glycemia, such as glycated hemoglobin (HbA1c) [5–8]. As these studies suggest, the assessment of 1,5-AG concentrations might also serve as a guide for glycemic control in surgical patients because surgical stressors are known to induce more dynamic changes in plasma glucose concentrations than those observed under normal conditions.

To our knowledge, few studies have investigated the effects of blood glucose on serum 1,5-AG concentrations in surgical patients. The aims of the present study were to investigate the relationship between plasma glucose concentrations and serum 1,5-AG concentrations in surgical patients, and to determine whether serum 1,5-AG concentrations are an accurate indicator of glycemic control in the perioperative period.

Patients and methods

The study was approved by the Research Ethics Committee of University of Miyazaki Hospital (Miyazaki, Japan). It was conducted in accordance with the Declaration of

Helsinki. All patients enrolled in the study provided written informed consent. This study was also registered with the UMIN Clinical Trials Registry (Reference, UMIN8457).

All participants in the study were inpatients of Miyazaki University Hospital. None of these patients had chronic kidney disease or severe liver cirrhosis, and none were pregnant. The exclusion criteria of this study included serum creatinine concentrations >2 mg/dL and aspartate aminotransferase (AST) and alanine transaminase (ALT) concentrations more than three times the upper limit of the normal range. DM was diagnosed according to criteria established by the Committee of the Japan Diabetes Society [9]. Of the 60 candidates, 3 were excluded from data analysis because they did not meet the inclusion criteria. The 57 patients enrolled in the study included 19 patients with type 2 DM (DM patients; 16 men and 3 women; age, 56–77 years) and 38 patients who did not have DM (non-DM patients; 28 men and 10 women; age, 52–82 years). Fourteen of the 19 DM patients were treated with conventional antidiabetic agents. Several types of insulin formulations were prescribed for 14 patients [6 patients, conventional insulin, 24.7 ± 12.7 units/day; 5 patients, neutral protamine Hagedorn (NPH) insulin, 19.6 ± 9.8 units/day; 3 patients, long-acting insulin, 8.7 ± 2.3 units/day (mean ± SD concentrations for each)]. The non-DM group comprised patients with no prior history of DM or hyperglycemia. The surgical procedure of hepatectomy was selected for these patients for the following reasons: (1) patients with hepatic cancer often have DM as a surgical complication; and (2) surgeons at our institution have expertise in performing hepatectomy. Therefore, a comparison of the two study groups was possible under identical surgical conditions and was more easily obtained than when the study was conducted with other types of surgical procedures.

All patients were required to fast overnight and discontinue their antidiabetic medications on the morning of surgery. A thoracic epidural catheter was inserted in the intervertebral thoracic space before induction of anesthesia. Next, anesthesia was induced with propofol and remifentanil injections. Tracheal intubation was performed by direct laryngoscopy and facilitated with a standard dose of rocuronium. Anesthesia was maintained with sevoflurane and remifentanil. Mechanical ventilation was adjusted to maintain extrapolated end-tidal carbon dioxide tension at 35–40 mmHg throughout the surgical procedure. During surgery, infusion rates were determined based on necessity, and sugar-based medications used were primarily 1% sugar-containing extracellular fluids (Table 1).

Plasma glucose concentrations were measured before surgery, during surgery (every 60 min in DM patients and every 90 min in non-DM patients), and at 24, 48, and 72 h after the initiation of surgery. These records were obtained from arterial blood samples using a gas analyzer (Radiometer ABL800, Copenhagen, Denmark). Subsequently, increase rates of plasma glucose concentrations were calculated individually using the following equation:

$$(\text{maximum concentration} - \text{minimum concentration})/\text{minimum concentration} \times 100$$

Blood samples for evaluation of 1,5-AG concentrations were obtained just before surgery and at 24, 48, and 72 h after the initiation of surgery from the remainder of the collected arterial blood samples used for standard anesthetic and intensive-care practices. Plasma was obtained by immediate centrifugation following blood collection and stored at −4°C until estimation of serum 1,5-AG concentrations (within 5 days). Thereafter, serum 1,5-AG concentrations were measured by an enzymatic method using a 1,5-AG auto liquid reagent and an automatic clinical analyzer (DM-JACK, Kyowa Medex, Tokyo, Japan). The decrease rate of serum 1,5-AG concentrations was calculated individually using the following equation:

(preoperative concentration − 24-h concentration)/preoperative concentration × 100

Statistical analyses

Data are described as the mean ± SD. The paired Student's *t*-test and Wilcoxon signed rank test were used to analyze the differences in plasma glucose concentrations (Fig 1a) and 1,5-AG concentrations (Figs 2a and 4). An unpaired Student's *t*-test and the Mann–Whitney U test were used to analyze differences in these concentrations among the total, non-DM, and DM patient groups (Table 1, Figs 1a, b and 2a, b). A linear regression model was used to regress the decrease rates of 1,5-AG concentrations with the increase rates of plasma glucose concentrations (Fig 3). Two-way repeated-measures analysis of variance (ANOVA) was used to analyze daily changes in serum 1,5-AG concentrations from just before surgery to 72 h after the initiation of surgery (Fig 4), and the values were considered statistically significant at $p < 0.05$. Statistical analyses were performed using SigmaPlot-12 (Systat Software, San Jose, CA, USA).

Results

Demographic and clinical characteristics of patients enrolled in the study are summarized in Table 1. The total number of fluid administrations, total number of glucose administrations for sugar-based medications, and urinary output for patients in the study revealed no significant differences among the groups. The mean value of preoperative HbA1c concentrations in the DM patient group (6.6 ± 0.9%) was significantly ($p < 0.01$) greater than that in the non-DM patient group (5.1 ± 0.4%).

Eleven of the 19 DM patients and 5 of the 39 non-DM patients were medicated with conventional insulin (Humulin R, Elli Lilly Japan, Kobe, Japan) against hyperglycemic episodes during surgery (total insulin dose, 18.4 ± 12.1 units in DM patients and 5.9 ± 3.0 units in non-DM patients).

Figure 1a displays the maximum and minimum plasma glucose concentrations during surgery in the total, non-DM and DM patient groups. The maximum concentration was significantly greater than the minimum concentration in each group. There was no significant difference in the minimum concentrations, but the maximum concentration in the DM group was significantly greater than that in the total ($p < 0.05$) and non-DM patient groups ($p < 0.01$). Moreover, the increase in plasma glucose concentrations during surgery was significantly greater in the DM patient group than in the non-DM patient group (Fig 1b).

Figure 2a presents serum 1,5-AG concentrations before surgery and at 24 h in the total, non-DM, and DM patient groups. The preoperative 1,5-AG concentrations in the total (15.7 ± 8.1 μg/mL) and non-DM (18.3 ± 7.4 μg/mL) patient groups were within the reference range; however, these concentrations were significantly lower in the DM patient group (10.7 ± 7.2 μg/mL) than in the total ($p < 0.05$) and non-DM ($p < 0.01$) patient groups. Moreover, these 1,5-AG concentrations had decreased significantly at 24 h in the total (11.9 ± 6.2 μg/mL), non-DM (13.9 ± 5.8 μg/mL), and DM (8.0 ± 4.9 μg/mL) patient groups. As demonstrated in Fig. 2b, the decrease rate of 1,5-AG concentrations in all groups revealed no significant difference.

The relationship between the decrease rates of 1,5-AG concentrations and the increase rates of plasma glucose concentrations in the three groups is presented in Fig. 3.

A significant correlation was observed in the total and the non-DM patient groups but not in the DM group.

The serum 1,5-AG concentrations of the three groups remained significantly low until the 72-h measurements were compared with respective preoperative concentrations (Fig. 4). Two-way repeated-measures ANOVA revealed that the postoperative 1,5-AG concentrations in the DM group were significantly ($p < 0.01$) lower than those in the other groups.

Discussion

When analyzed among all patients, plasma glucose concentrations increased significantly during hepatectomy and serum 1,5-AG concentrations decreased after surgery. In addition, linear regression analysis revealed a weak but significant correlation between the decrease rate of 1,5-AG concentrations and the increase rate of plasma glucose concentrations, thereby suggesting that the measurement of 1,5-AG concentrations may be a useful approach for evaluating glycemic control during surgical anesthesia. However, when analyzed more specifically with regard to the presence or absence of DM, regression analyses revealed a strong correlation between the decrease rate of 1,5-AG concentrations and the increase rate of plasma glucose concentrations among patients in the non-DM patient group but not in the DM patient group. These results suggest that serum 1,5-AG concentrations decrease significantly in proportion to increase in plasma glucose concentrations in patients without diabetes, but these concentrations are less sensitive to such changes in patients with diabetes.

It is well established that glycemic control helps to reduce (or prevent) complications in surgical patients [10–11]. Currently, measurements such as HbA1c, glycated albumin, fructosamine, and 1,5-AG concentrations are used as clinical markers of glycemic control. However, HbA1c concentrations yield an estimate of glycemia for the previous 2–3 months, whereas glycated albumin and fructosamine represent an estimate of glycemia for the previous 2–3 weeks [12]. Thus, the response rates of these parameters are too slow for the evaluation of intraoperative glycemic metabolism. Conversely, decrease in serum 1,5-AG concentrations have been reported to be closely related to hyperglycemia (even if the hyperglycemic episodes are transient) [13]. In addition, a decrease in 1,5-AG concentrations has been observed to closely reflect the extent of short-term glycosuria in a rat model [14]. Therefore, measurement of 1,5-AG concentrations should be considered the most reliable tool among glycemic markers to detect intraoperative glycemic changes in surgical patients.

1,5-AG is a major polyol detected in human serum and cerebrospinal fluid [15–16]. It originates mainly from foods, is well absorbed in the intestine, slightly degraded, and is subsequently metabolized in the body [17]. In general, 1,5-AG is freely filtered in the kidney with 99.9% being reabsorbed by the renal tubules [6]. This property ensures a stable concentration of 1,5-AG in the plasma of healthy individuals. However, persistent glycosuria in the setting of severe hyperglycemia leads to a decrement in the plasma pool and tissue pool of 1,5-AG by competitive inhibition of glucose reabsorption in the renal tubules [6]. It has been reported that if glucose concentrations exceed 160–180 mg/dL, reabsorption of 1,5-AG declines with subsequent reduction in serum concentrations of 1,5-AG [6]; thus, changes in 1,5-AG concentrations might reflect hyperglycemic episodes over a short period [7]. It is recognized among anesthesiologists that plasma glucose concentrations are often increased due to surgical stress. In fact, in 86% (49 of 57 patients) patients of the present study, the maximum plasma glucose concentrations during surgery were >180 mg/dL. Thus, we suggest that serum 1,5-AG concentrations might be affected by hyperglycemia during surgery.

The reference value for plasma 1,5-AG concentrations in a healthy human ranges from 14.4 to 30.2 μg/mL and in poorly-controlled DM it is <14.0 μg/mL [18]. However, according to Won et al., in outpatient settings, plasma 1,5-AG concentrations do not precisely reflect short-term glycemic states in patients with severe DM because the baseline concentrations of 1,5-AG are low [19]. Accordingly, 1,5-AG concentrations may play a weak role as an intraoperative glycemic marker in patients with chronic hyperglycemia. For this reason, this study analyzed this data independently between patients with and without diabetes.

To clarify the metabolic correlation between plasma glucose and serum 1,5-AG concentrations during surgery, a regression analysis was performed by comparison of each rate that changed during surgery. In the non-DM patient group of the present study, a significant correlation was observed between the decrease rate of 1,5-AG concentrations and the increase rate of plasma glucose concentrations. This finding suggests that 1,5-AG concentrations decrease according to fluctuations in glucose concentrations during surgery. Hence, 1,5-AG could be a biochemical marker for short-term glycemic changes in surgical patients without DM. On the other hand, this association was not observed in the DM patient group, thereby suggesting that 1,5-AG concentrations do not decrease in proportion to the increase in plasma glucose concentrations. Indeed, the increase rate of plasma glucose concentrations was significantly greater in the DM patient group than in the non-DM patient group; thus, the decrease rate of 1,5-AG concentrations would be expected to be greater in DM patients than in non-DM patients. Nevertheless, such a difference was not evident in the

DM patient group. Considering the fact that the preoperative 1,5-AG concentrations in 70% (13 of 19) DM patients were below the reference range, we concluded that the preoperative serum 1,5-AG concentrations observed in the DM patient group were too low to initiate adequate urinary excretion of 1,5-AG against the hyperglycemic episodes during surgery. These results were in agreement with the abovementioned report by Dworacka et al. [19].

In DM and non-DM patients, decreased 1,5-AG concentrations were observed until at least 72 h after the initiation of surgery. It has been reported that the average daily increase in serum 1,5-AG concentrations is constant at about 0.3 μg/mL, and is not influenced by treatment, age, body weight, or duration of DM [20]. In addition, the normalization of 1,5-AG concentrations from depleted states has been believed to require approximately 5 weeks even under continuous normoglycemic conditions [20, 21]. Thus, the recovery of 1,5-AG concentrations in our surgical patients may have been slow, with a time scale of several weeks after feeding is initiated.

This was the first study focusing on the association between 1,5-AG concentrations and plasma glucose concentrations in surgical patients, but it had several limitations. These included the small differences in sex and age [22], the inability to compare 1,5-AG concentrations with glycosuria [14], and the effects of anesthetic management, including insulin therapy. However, the main limitation of this study was the relatively small number of patients, which questions the validity of our further mentioned conclusion. Thus, it will be necessary to examine these factors with a larger study cohort.

In summary, we studied the effects of plasma glucose concentrations on serum 1,5-AG concentrations in surgical patients. Serum 1,5-AG concentrations decreased significantly in proportion to increase in plasma glucose concentrations in non-DM patients. This finding suggests that the measurement of postoperative 1,5-AG concentrations may be a useful approach for evaluating glycemic control in surgical patients with normal glycemic metabolism. However, the 1,5-AG concentrations in DM patients appeared to be less sensitive to intraoperative glycemic variation, probably because preoperative 1,5-AG concentrations were already low. Although the availability of a short-term marker of glycemic control would be a valuable tool for monitoring glucose metabolism at all stages of anesthesia, larger studies are warranted, which address these parameters of 1,5-AG in surgical patients.

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Figure legends

Fig1 (a) Maximum (max) and minimum (min) plasma glucose concentrations recorded during hepatectomy among all patients and patients with and without diabetes mellitus (total, DM, and non-DM patient groups, respectively). $^{**}p < 0.01$ compared with minimum concentrations in each group. (b) Increase rates in plasma glucose concentrations during surgery in the total, non-DM and DM patient groups. $^{\#}p < 0.05$ compared with non-DM patients.

Fig2 (a) Serum 1,5-anhydroglucitol (1,5-AG) concentrations before surgery (Pre) and 24 h (24h) after the initiation of surgery among all patients and patients with and without diabetes mellitus (total, DM, and non-DM patient groups, respectively). $^{**}p < 0.01$ compared with preoperative concentrations in each group. (b) Decrease rate in 1,5-AG concentrations from before surgery to 24 h in the total, non-DM, and DM patient groups. There were no significant differences between the groups.

Fig3 Relationship between decrease rate in 1,5-anhydroglucitol (1,5-AG) concentrations and increase rate in plasma glucose concentrations in all patients and patients with and without diabetes mellitus (total, DM, and non-DM patient groups, respectively). A significant correlation was obtained in the total and non-DM patient groups but not in the DM patient group.

Fig4 Changes in 1,5-anhydroglucitol (1,5-AG) concentrations before surgery (pre) to 72 h after the initiation of surgery among all patients and patients with and without diabetes mellitus (total, DM and non-DM patient groups, respectively). $^{**}p < 0.01$ compared with preoperative concentrations in each group (paired Student's *t*-test). Two-way repeated measure analysis of variance (ANOVA) revealed that serum 1,5-AG concentrations were significantly ($p < 0.01$) lower in the DM patient group than in the total and non-DM patient groups

Figure1

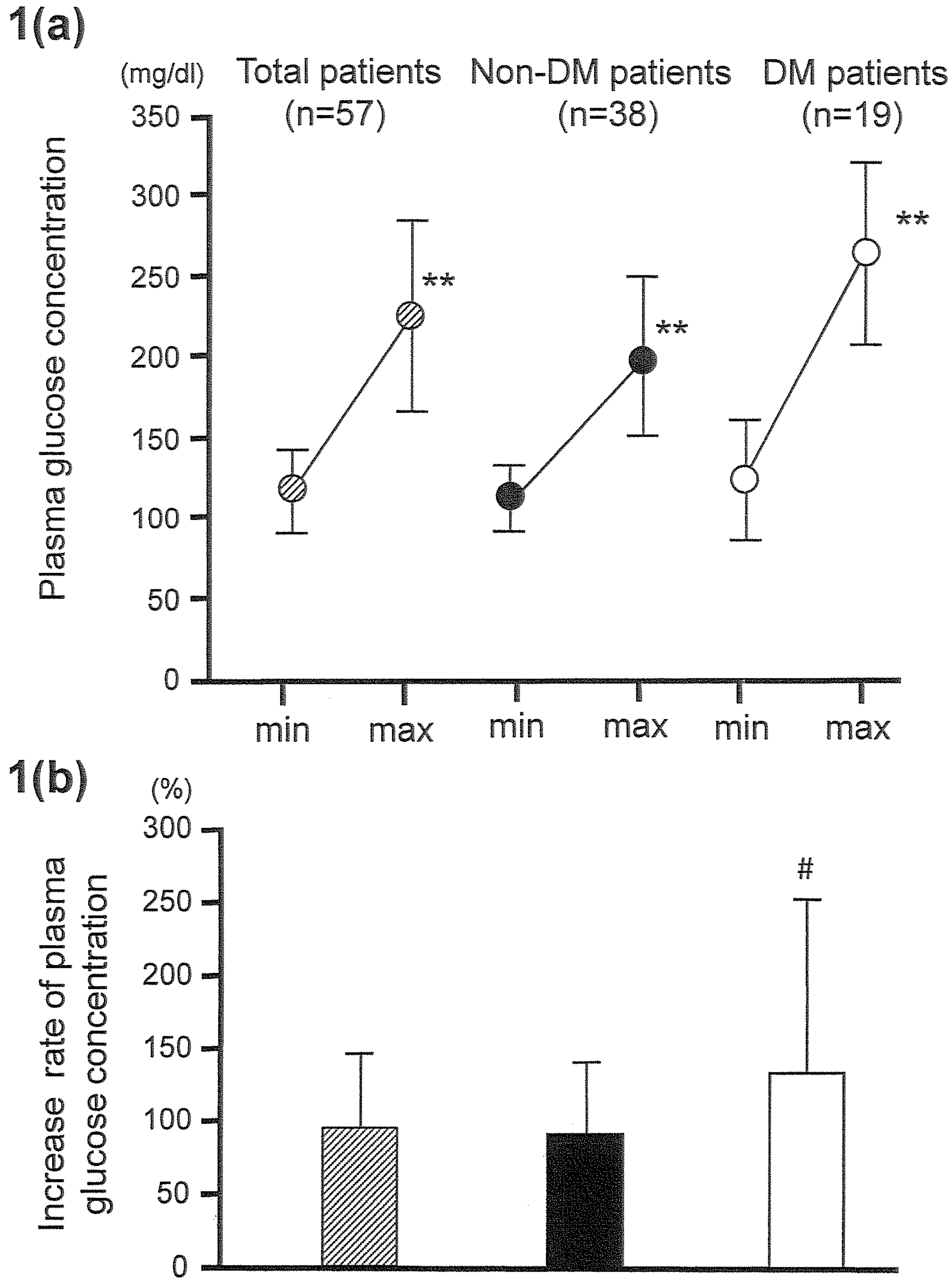
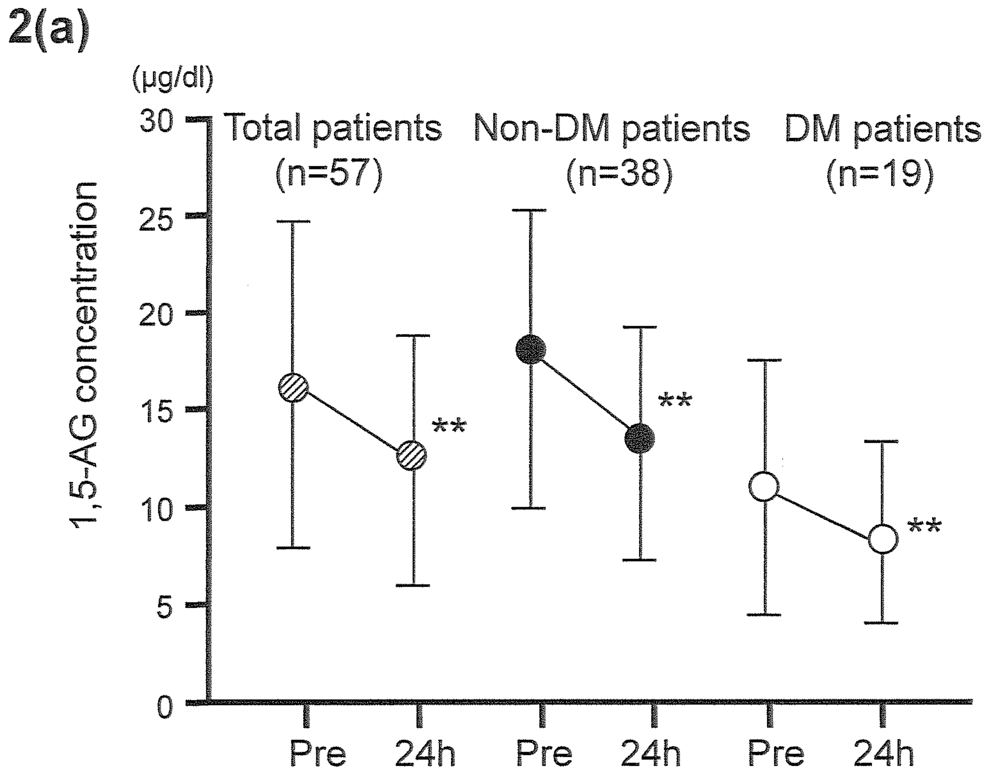

1(a)
(mg/dl)
Total patients (n=57)
Non-DM patients (n=38)
DM patients (n=19)
Plasma glucose concentration
350
300
250
200
150
100
50
0
**
**
**
min
max
min
max
min
max
1(b)
(%)
Increase rate of plasma glucose concentration
300
250
200
150
100
50
0
#

Figure2


2(a)
(μg/dl)
1,5-AG concentration
30
25
20
15
10
5
0
Total patients
(n=57)
Non-DM patients
(n=38)
DM patients
(n=19)
**
**
**
Pre
24h
Pre
24h
Pre
24h

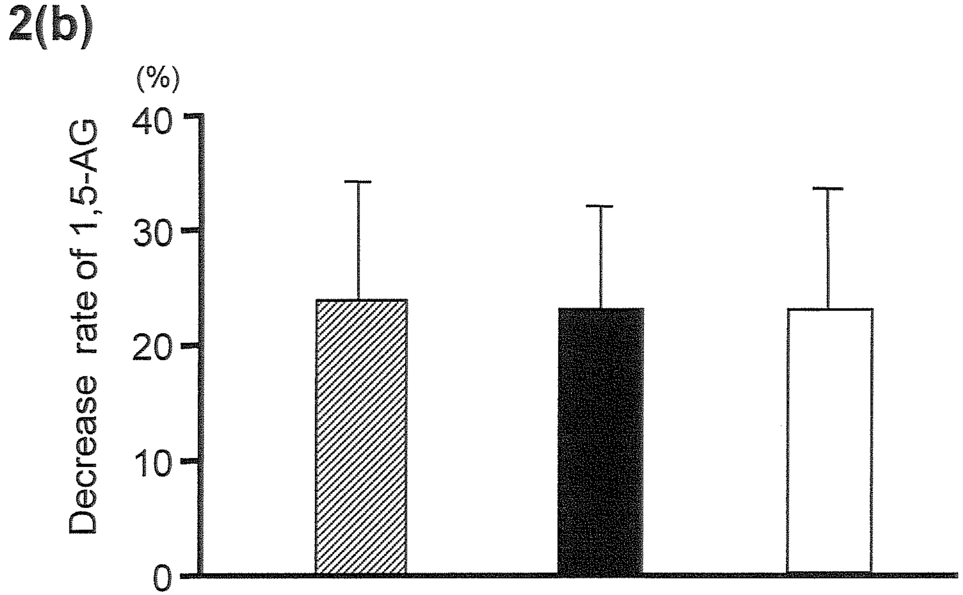

2(b)
(%)
Decrease rate of 1,5-AG
40
30
20
10
0

Figure3

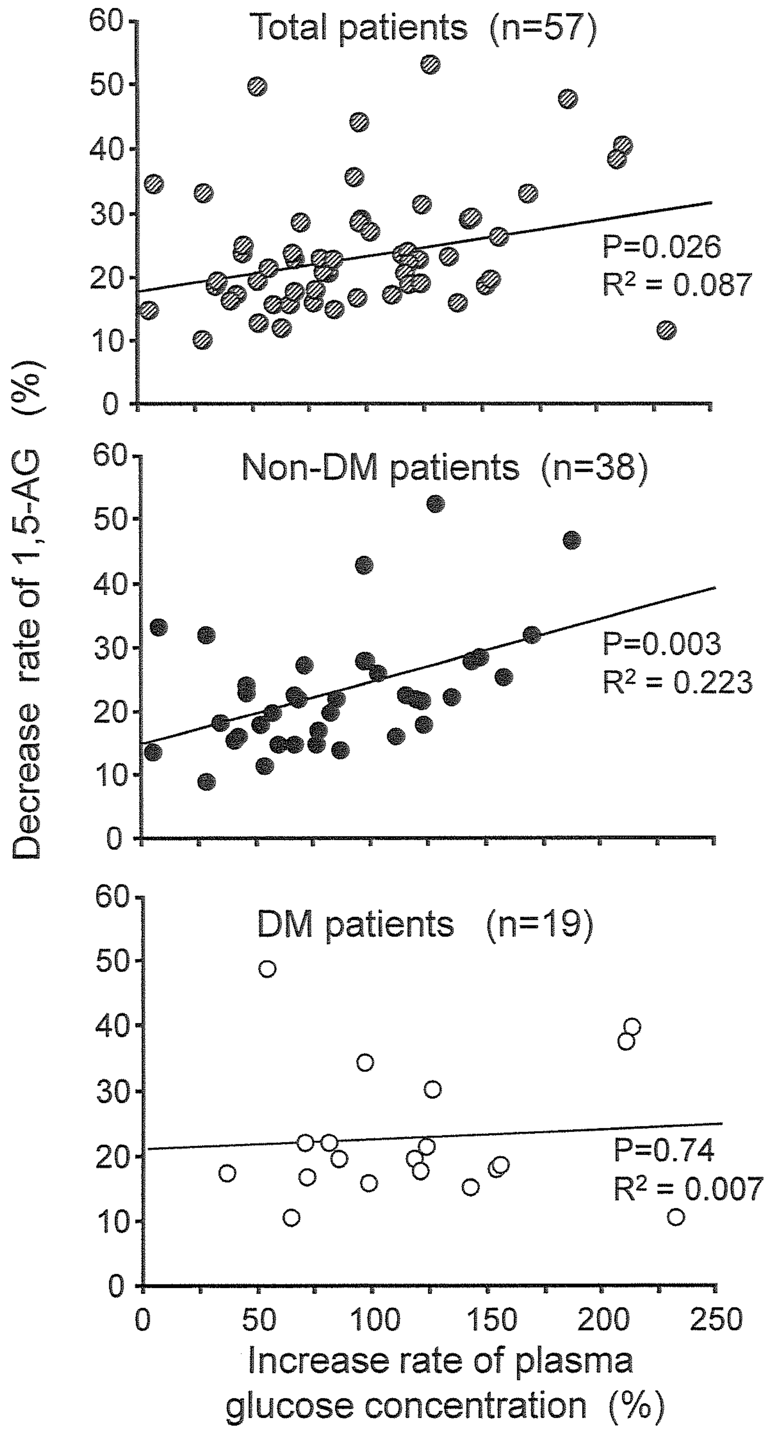

Total patients (n=57)
P=0.026
R² = 0.087
Non-DM patients (n=38)
P=0.003
R² = 0.223
DM patients (n=19)
P=0.74
R² = 0.007
Decrease rate of 1,5-AG (%)
Increase rate of plasma glucose concentration (%)
0
10
20
30
40
50
60
0
50
100
150
200
250

Figure4

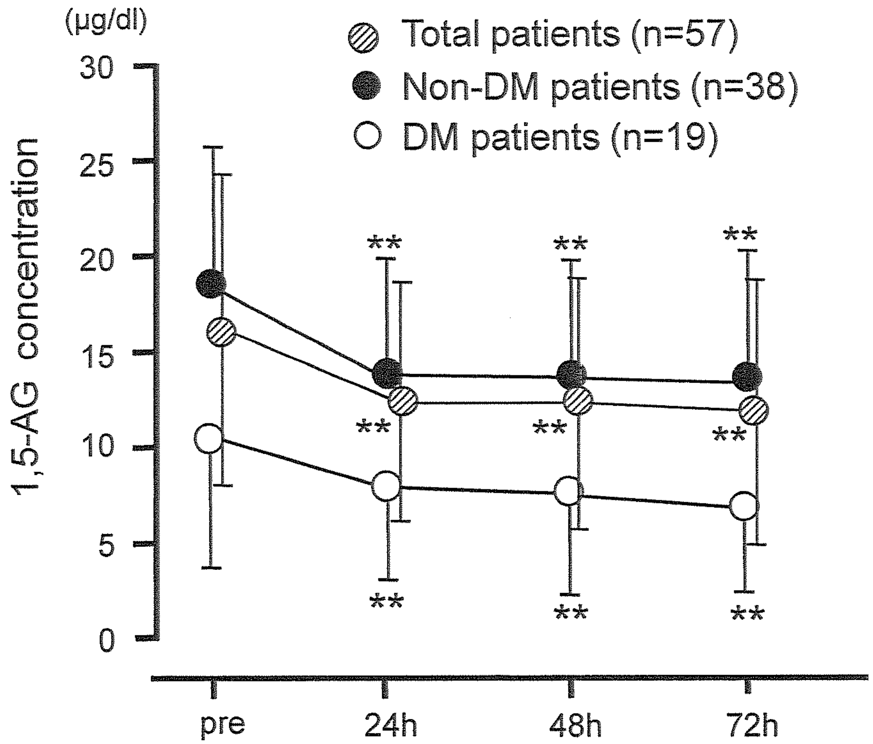

(μg/dl)
Total patients (n=57)
Non-DM patients (n=38)
DM patients (n=19)
1,5-AG concentration
30
25
20
15
10
5
0
**
**
**
**
**
**
**
**
**
pre
24h
48h
72h

Table 1

Table 1: Demographic and Variables during surgery

Variables	Total patients (n=57)	Non-diabetic patients (n=38)	Diabetic patients (n=19)
Age (y)	66.9±10.0	65.9±10.9	68.9±7.9
Male/female (n/n)	44/13	28/10	16/3
Height (cm)	161.0±7.2	159.9±7.1	163.2±7.2
Weight (kg)	59.4±9.0	58.4±9.3	61.6±8.2
Body mass index (kg/m^2)	22.9±3.2	22.8±3.2	23.2±3.2
Length of anesthesia (min)	551.8±127.9	537.2±142.8	581.1±87.5
Length of surgery (min)	463.3±122.4	450.4±135.1	489.1±89.7
Estimated blood loss (ml)	1448.4±1167.8	1425.5±1296.9	1494.2±884.3
Total infusion amount (ml)	5917.5±2209.7	5717.8±2449.4	6317.1±1614.5
Total glucose administration (g)	30.6±21.9	32.2±24.9	27.3±14.5
Total urine output (ml)	1423.5±1155.0	1450.7±1180.2	1369.2±1132.7

Values are mean ± SD.