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# Serum 1,5-anhydroglucitol levels slightly increase rather than decrease after a glucose load in subjects with different glucose tolerance status

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## Abstract

*Aims* Previous studies showed that serum 1,5-anhydroglucitol (1,5-AG) levels are significantly reduced in patients with diabetes mellitus (DM). However, it remains unclear how 1,5-AG levels acutely change in response to a glucose load. This study explored acute changes in 1,5-AG levels after a glucose load and the related influencing factors in individuals with differing degrees of glucose tolerance.

*Methods* A total of 681 participants (353 without DM and 328 with DM) without a prior history of DM were enrolled. All participants underwent an oral glucose tolerance test. Fasting and postload (30, 60, 120, and 180 min) levels of plasma glucose, serum 1,5-AG, and insulin were measured.

*Results* In all participant groups, serum 1,5-AG levels were slightly elevated after a glucose load and reached peak values at 120 min after loading (all $P < 0.05$). Regression analysis showed that body weight was negatively associated with the difference between peak and baseline 1,5-AG levels ($\Delta$1,5-AG, standardized $\beta = -0.119$, $P < 0.01$). A strong and positive association between 1,5-AG$_0$ and $\Delta$1,5-AG was also found independent of other confounding factors (standardized $\beta = 0.376$, $P < 0.01$). The ratio of the $\Delta$1,5-AG to the 1,5-AG$_0$ was higher in DM patients (7.3% [3.4–11.5%]) than in those without DM (6.2% [3.6–9.2%]).

*Conclusions* In contrast to the established decline in 1,5-AG levels with long-term hyperglycemia, the present study showed that serum 1,5-AG levels slightly increased by 6–7% after a glucose load. Further studies in different 1,5-AG transport models are needed to investigate the relevant metabolic pathways.

**Keywords** 1,5-Anhydroglucitol · Oral glucose tolerance test · Plasma glucose · Insulin

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## Introduction

1,5-Anhydroglucitol (1,5-AG), a six-carbon chain monosaccharide produced primarily during ingestion, is a 1-deoxy form of glucopyranose with a structure similar to glucose. Importantly, patients with diabetes mellitus (DM) exhibit significantly lower levels of 1,5-AG than normoglycemic individuals. Based on its ability to accurately reflect glucose control over a period of 1–2 weeks [1, 2], 1,5-AG was approved by the US Food and Drug Administration (FDA) in 2003 as a short-term marker of glycemic control [3, 4]. Measurement of the 1,5-AG level is valuable in assessing short-term and postprandial glycemic excursions [5, 6], especially in individuals with a glycated hemoglobin $A_{1c}$ (HbA$_{1c}$) level less than 8% (64 mmol/mol) [7, 8].

With long-term hyperglycemia, large amounts of urinary glucose are persistently filtered off, which competitively inhibits reabsorption of l,5-AG in the renal proximal tubules [9]. This leads to an increase in the level of excreted l,5-AG and a decrease in the serum 1,5-AG level in patients with DM. Few studies have explored the specific physiological roles of 1,5-AG as well as the corresponding metabolic pathways, specifically in relation to the acute changes in serum 1,5-AG levels after a glucose load, and the results have been inconclusive due to small sample sizes. For example, Akanuma et al. [10] found that 1,5-AG levels remained stable after a glucose load, whereas Goto et al. [11] reported that 1,5-AG levels were significantly increased at 90, 120, and 180 min during an oral glucose tolerance test (OGTT) in 77 healthy Japanese individuals. Therefore, the goal of the present study was to explore the acute changes in serum 1,5-AG levels after glucose loading in individuals with varied degrees of glucose tolerance and to identify the related influencing factors, for the purpose of better understanding the role of 1,5-AG in metabolism and supporting further studies of its transport.

## Materials and methods

### Study population

The study population included 681 individuals, including 310 men and 371 women (age range 21–78 years), who were treated in the clinic of the Department of Endocrinology and Metabolism of Shanghai Jiao Tong University Affiliated Sixth People's Hospital between January 2014 and January 2016. All participants had no history of DM, history of diet control, or current use of hypoglycemic agents. The study population was restricted to those without subtotal gastrectomy, thyroid dysfunction, kidney disease, chronic liver disease, tumors, mental disorders, cystic fibrosis, acute infection, pregnancy, or a history of use of some traditional Chinese medicines such as Polygala Tenuifolia and Senega syrup therapy. This study was approved by the Ethics Committee of Shanghai Jiao Tong University Affiliated Sixth People's Hospital. Informed consent was provided by all participants prior to enrollment.

### Collection of clinical information

Well-trained investigators conducted a questionnaire survey that included questions about participants' history of past and present illnesses and medication use. Blood pressure, height, and body weight were measured, and body mass index (BMI) was calculated as $weight/height^2$ $(kg/m^2)$.

### Biochemical measurements

Blood samples from all subjects were obtained in the morning after a 10-h overnight fast to measure the levels of fasting plasma glucose ($PG_0$), fasting serum 1,5-AG ($1,5-AG_0$), fasting serum insulin ($INS_0$), and $HbA_{1c}$. A 75-g OGTT was administered to each outpatient to assay the postload levels of plasma glucose ($PG_{30}$, $PG_{60}$, $PG_{120}$, and $PG_{180}$), serum 1,5-AG ($1,5-AG_{30}$, $1,5-AG_{60}$, $1,5-AG_{120}$, and $1,5-AG_{180}$), and serum insulin ($INS_{30}$, $INS_{60}$, $INS_{120}$, and $INS_{180}$) at 30, 60, 120, and 180 min, respectively. Plasma glucose levels were immediately obtained by the glucose oxidase method (Kehua Biological Engineering Co., Ltd., Shanghai, China) using the Glamour 2000 biochemical autoanalyzer. Serum 1,5-AG levels were measured by an enzymatic method (GlycoMark[TM]; GlycoMark Inc., New York, NY, USA) on a 7600–120 autoanalyzer (Hitachi, Tokyo, Japan) with inter- and intra-assay coefficients of variation (CV) of 1.54–3.03 and 0.83–2.44%, respectively. $HbA_{1c}$ was detected by high-pressure liquid chromatography (Variant II hemoglobin analyzer; Bio-Rad, Hercules, CA, USA) with inter- and intra-assay CV of 0.75–3.39 and 0.55–2.58%, respectively. Electrochemiluminescence immunoassay was used to quantify the serum insulin levels on a Cobas e 411 analyzer (Roche Diagnostics GmbH, Mannheim, Germany) with inter- and intra-assay CV of 2.50 and 1.70%, respectively.

### Diagnostic criteria

DM and impaired glucose regulation (IGR) were diagnosed according to the 1999 World Health Organization (WHO) criteria [12]. The 1998 WHO standards were used to classify BMI: participants with BMI $\geq 25$ kg/m$^2$ were classified as overweight/obesity [13].

### Calculation of differences in postload 1,5-AG levels

The difference between peak and baseline 1,5-AG levels ($\Delta 1,5-AG$) was used to evaluate the range of variation in postload 1,5-AG levels. Then, the ratio of $\Delta 1,5-AG$ to the baseline 1,5-AG levels ($\Delta 1,5-AG/1,5-AG_0$) was expressed as a percentage and used to assess the relative differences in postload 1,5-AG levels.

### Statistical analysis

SPSS version 19.0 (SPSS, Inc., Chicago, IL, USA) was used for statistical analysis. Based on a normality test, normally distributed data are presented as mean ± standard deviation values, and skewed data are presented as median with interquartile ranges. Pair analyses were carried out using the paired Student's *t* test and the Wilcoxon signed-rank sum test. Intergroup comparisons were

conducted with the unpaired Student's $t$ test, Kruskal–Wallis test, and Chi-squared test for continuous data with a normal distribution, continuous data with a skewed distribution, and categorical variables, respectively. Spearman correlation analysis and multiple stepwise regression analysis were conducted to identify independent factors influencing $\Delta 1,5$-AG levels. A two-tailed $P$ value < 0.05 was considered to be statistically significant.

## Results

### Clinical characteristics of outpatient study participants

The average age of the 681 study participants was 53 years (39–61 years), and the average $HbA_{1c}$ level was 5.9% (5.5–6.5%) (41 mmol/mol [37–48 mmol/mol]). Among the entire study population, 184 participants exhibited normal glucose tolerance (NGT, 27.0%, 59 men and 125 women), 169 presented with IGR (24.8%, 75 men and 94 women), and 328 were diagnosed with DM (48.2%, 176 men and 152 women). Compared with the NGT group, the DM and IGR groups showed higher values of age, systolic blood pressure, body weight, BMI, $HbA_{1c}$, $PG_0$, $PG_{30}$, $PG_{60}$, $PG_{120}$, and $PG_{180}$ (all $P < 0.05$), along with lower levels of $INS_0$, $INS_{30}$, $INS_{120}$, and $INS_{180}$ (all $P < 0.05$; Table 1).

The $1,5$-$AG_0$, $1,5$-$AG_{30}$, $1,5$-$AG_{60}$, $1,5$-$AG_{120}$, and $1,5$-$AG_{180}$ levels were significantly lower in the DM group than in the NGT and IGR groups ($P < 0.01$). However, the serum 1,5-AG levels did not differ significantly between the NGT and IGR groups ($P > 0.05$).

### Acute changes in serum 1,5-AG levels after OGTT

Postload 1,5-AG levels at each time point were slightly higher than baseline levels and reached peak values at 120 min in all three groups (all $P < 0.01$; Fig. 1). The same results were obtained in separate analyses for men and women as well as for overweight/obesity and non-overweight/non-obesity participants.

The mean $\Delta 1,5$-AG values were 1.4 μg/mL (0.7–2.3 μg/mL), 1.4 μg/mL (0.7–2.2 μg/mL), and 0.9 μg/mL (0.5–1.4 μg/mL) for the NGT, IGR, and DM groups, respectively. These results demonstrated that the $\Delta 1,5$-AG was significantly lower in patients with DM than in individuals with IGR or NGT (both $P < 0.01$), whereas the $\Delta 1,5$-AG did not differ significantly between those with IGR and NGT ($P = 0.400$).

### Factors independently associated with $\Delta 1,5$-AG

Spearman correlation analysis revealed that the $\Delta 1,5$-AG was negatively associated with body weight, BMI, $HbA_{1c}$,

$INS_0$, $PG_0$, $PG_{30}$, $PG_{60}$, $PG_{120}$, and $PG_{180}$ (all $P < 0.05$). Further multiple stepwise regression models were performed to identify factors independently affecting the range of variation in postload 1,5-AG levels, with $\Delta 1,5$-AG defined as the dependent variable. Model 1 included gender, age, BMI, $HbA_{1c}$, $PG_0$, $PG_{30}$, $PG_{60}$, $PG_{120}$, $PG_{180}$, and $INS_0$ as independent variables and showed that $\Delta 1,5$-AG was independently related to $PG_{120}$, BMI, and age (standardized $\beta = -0.261$, $-0.109$, and 0.131, respectively; all $P < 0.01$). In Model 2, body weight was included as independent variable to replace BMI, and the results indicated that $\Delta 1,5$-AG was significantly associated with $PG_{120}$, body weight, and age (standardized $\beta = -0.254$, $-0.136$, and 0.121, respectively; all $P < 0.01$). A comparison of the standardized $\beta$ values for BMI and body weight revealed that body weight had a more significant negative impact on $\Delta 1,5$-AG. Postload 1,5-AG excursions were inversely associated with body weight.

When the $1,5$-$AG_0$ level was added to Model 3, the results showed that in addition to body weight (standardized $\beta = -0.119$, $P < 0.01$), $1,5$-$AG_0$ positively influenced $\Delta 1,5$-AG (standardized $\beta = 0.376$, $P < 0.01$; Table 2). Furthermore, when Model 3 was performed separately for participants with and without DM, the results showed $1,5$-$AG_0$, body weight, and age all contributed to $\Delta 1,5$-AG in individuals without DM (standardized $\beta = 0.372$, $-0.109$, and 0.105, respectively; all $P < 0.05$; Fig. 2), and that $1,5$-$AG_0$, body weight, and $PG_{120}$ contributed to $\Delta 1,5$-AG in patients with DM (standardized $\beta = 0.189$, $-0.142$, and $-0.148$, respectively; all $P < 0.05$; Fig. 2).

### Effect of baseline serum 1,5-AG levels on $\Delta 1,5$-AG

As the regression analysis models showed, the baseline $1,5$-AG level was the main factor independently related to postload 1,5-AG excursions. The $\Delta 1,5$-AG/$1,5$-$AG_0$ was 6.6% (3.5–10.1%) among all participants and higher in DM patients than in participants without DM (7.3% [3.4–11.5%] vs. 6.2% [3.6–9.2%], $P < 0.05$). The $\Delta 1,5$-AG/$1,5$-$AG_0$ differed significantly neither between men and women (6.6% [3.4–10.7%] vs. 6.5% [3.6–9.5%]) nor between overweight/obesity and non-overweight/non-obesity participants (6.5% [3.5–10.7%] vs. 6.6% [3.4–9.8%]).

## Discussion

The current study provides the first analysis of acute changes in serum 1,5-AG levels after a glucose load and the related influencing factors in a Chinese population. The results showed that serum 1,5-AG levels were slightly elevated after a glucose load rather than reduced. These results held true for individuals with different glucose

**Table 1** Demographic and clinical characteristics of study participants

| Variable | Total (n = 681) | NGT (n = 184) | IGR (n = 169) | DM (n = 328) |
|---|---|---|---|---|
| Gender (men/women) | 310/371 | 59/125 | 75/94* | 176/152** |
| Age (years) | 53 (39–61) | 42 (32–58) | 51 (38–61)** | 56 (46–62)**$^{\dagger\dagger}$ |
| Body weight (kg) | 67.5 (60.0–75.0) | 62.0 (56.1–70.8) | 69.5 (60.0–76.0)** | 70.0 (62.0–78.8)** |
| BMI (kg/m$^2$) | 24.7 ± 3.3 | 23.6 ± 3.3 | 24.6 ± 3.4** | 25.3 ± 3.2**$^{\dagger}$ |
| Systolic blood pressure (mm Hg) | 130.0 (118.5–141.0) | 121.0 (112.0–132.8) | 130.0 (118.0–140. 0)** | 134.0 (124.0–147.8)** $^{\dagger\dagger}$ |
| Diastolic blood pressure (mm Hg) | 79.0 (72.0–85.0) | 75.0 (70.0–82.0) | 77.0 (71.0–85.0) | 82.5 (75.0–88.0)**$^{\dagger\dagger}$ |
| HbA$_{1c}$ (%) | 5.9 (5.5–6.5) | 5.5 (5.2–5.7) | 5.8 (5.5–6.0)** | 6.5 (6.0–6.9)**$^{\dagger\dagger}$ |
| HbA$_{1c}$ (mmol/mol) | 41 (37–48) | 37 (33–39) | 40 (37–42)** | 48 (42–52)**$^{\dagger\dagger}$ |
| PG$_0$ (mmol/L) | 6.3 (5.5–7.3) | 5.4 (5.0–5.7) | 6.1 (5.5–6.4)** | 7.4 (6.8–8.2)**$^{\dagger\dagger}$ |
| PG$_{30}$ (mmol/L) | 10.8 (9.3–12.7) | 8.8 (8.0–9.6) | 10.3 (9.5–11.4)** | 12.6 (11.2–14.1)**$^{\dagger\dagger}$ |
| PG$_{60}$ (mmol/L) | 12.6 (9.6–15.8) | 8.6 (7.1–9.8) | 11.7 (9.8–13.1)** | 15.8 (13.8–17.5)**$^{\dagger\dagger}$ |
| PG$_{120}$ (mmol/L) | 9.7 (7.0–14.3) | 6.2 (5.3–6.9) | 8.9 (8.0–9.7)** | 14.4 (12.2–17.0)**$^{\dagger\dagger}$ |
| PG$_{180}$ (mmol/L) | 6.4 (4.7–9.3) | 4.7 (3.7–5.8) | 5.5 (4.5–6.9)** | 9.4 (7.2–12.1)**$^{\dagger\dagger}$ |
| 1,5-AG$_0$ (μg/mL) | 18.9 (12.6–26.3) | 23.3 (16.6–30.2) | 22.5 (15.9–28.8) | 15.1 (8.9–20.8)**$^{\dagger\dagger}$ |
| 1,5-AG$_{30}$ (μg/mL) | 19.2 (12.8–26.4) | 24.5 (17.4–30.3) | 23.1 (16.1–29.1) | 15.1 (9.2–20.9)**$^{\dagger\dagger}$ |
| 1,5-AG$_{60}$ (μg/mL) | 19.5 (13.2–27.1) | 24.9 (17.4–31.2) | 23.1 (16.2–29.7) | 15.5 (9.2–21.2)**$^{\dagger\dagger}$ |
| 1,5-AG$_{120}$ (μg/mL) | 19.8 (13.3–27.2) | 24.9 (17.1–31.6) | 24.2 (16.2–30.2) | 15.9 (9.3–21.8)**$^{\dagger\dagger}$ |
| 1,5-AG$_{180}$ (μg/mL) | 19.6 (13.2–27.2) | 24.9 (17.1–31.1) | 23.8 (16.1–30.3) | 15.5 (8.9–21.5)**$^{\dagger\dagger}$ |
| INS$_0$ (mU/L) | 9.6 (6.8–14.0) | 7.7 (5.5–10.9) | 9.1 (6.5–12.6)** | 11.2 (7.8–16.2)**$^{\dagger\dagger}$ |
| INS$_{30}$ (mU/L) | 51.8 (32.5–82.8) | 70.8 (48.2–119.5) | 64.8 (39.7–100.6)* | 39.8 (25.3–59.2)**$^{\dagger\dagger}$ |
| INS$_{60}$ (mU/L) | 73.2 (49.8–107.3) | 82.5 (55.0–115.2) | 78.8 (55.9–116.7) | 65.9 (43.2–96.5)**$^{\dagger\dagger}$ |
| INS$_{120}$ (mU/L) | 77.9 (50.2–118.4) | 61.1 (41.8–92.1) | 88.2 (53.9–135.2)** | 83.7 (54.9–132.1)** |
| INS$_{180}$ (mU/L) | 32.6 (17.5–58.0) | 21.6 (11.2–38.2) | 28.4 (15.7–47.6)** | 45.5 (25.1–71.8)**$^{\dagger\dagger}$ |
| Δ1,5-AG (μg/mL) | 1.1 (0.6–1.9) | 1.4 (0.7–2.3) | 1.4 (0.7–2.2) | 0.9 (0.5–1.4)**$^{\dagger\dagger}$ |
| Δ1,5-AG/1,5-AG$_0$ (%) | 6.6 (3.5–10.1) | 6.3 (3.8–9.3) | 6.1 (3.4–9.1) | 7.3 (3.4–11.5)$^{\dagger}$ |

Data are presented as mean ± standard deviation or median (interquartile range)

Δ1,5-AG, range of variation in postload 1,5-anhydroglucitol levels; 1,5-AG$_0$, fasting 1,5-anhydroglucitol; 1,5-AG$_{30}$, 30-min postload 1,5-anhydroglucitol; 1,5-AG$_{60}$, 60-min postload 1,5-anhydroglucitol; 1,5-AG$_{120}$, 120-min postload 1,5-anhydroglucitol; 1,5-AG$_{180}$, 180-min post-load 1,5-anhydroglucitol; BMI, body mass index; DM, diabetes mellitus; HbA$_{1c}$, glycated hemoglobin A$_{1c}$; IGR, impaired glucose regulation; INS$_0$, fasting insulin; INS$_{30}$, 30-min postload insulin; INS$_{60}$, 60-min postload insulin; INS$_{120}$, 120-min postload insulin; INS$_{180}$, 180-min postload insulin; NGT, normal glucose tolerance; PG$_0$, fasting plasma glucose; PG$_{30}$, 30-min postload plasma glucose; PG$_{60}$, 60-min postload plasma glucose; PG$_{120}$, 120-min postload plasma glucose; PG$_{180}$, 180-min postload plasma glucose

* $P < 0.05$ versus NGT group; ** $P < 0.01$ versus NGT group; $^{\dagger}$ $P < 0.05$ versus IGR group, $^{\dagger\dagger}$ $P < 0.01$ versus IGR group

metabolism statuses. Regression analysis showed that in addition to the independent negative association with body weight, the baseline 1,5-AG level was an independent factor more strongly contributing to a larger range of variation in the postload 1,5-AG levels. The 1,5-AG levels increased by 6–7% from the baseline 1,5-AG levels, and no association was found between insulin levels and the Δ1,5-AG.

In addition to research demonstrating that 1,5-AG can accurately and rapidly reflect glucose control over a period of 1–2 weeks [14, 15], previous studies have suggested that 1,5-AG is superior to glycated albumin (GA) and HbA$_{1c}$ for the evaluation of postprandial glucose variability. Sun et al. [16] found that 1,5-AG, rather than HbA$_{1c}$ and GA, is significantly correlated with postprandial glucose excursions and the postprandial incremental area under the curve in moderately and well-controlled patients. Pramodkumar et al. [17] measured fasting serum levels of 1,5-AG, fructosamine, and HbA$_{1c}$ in Asian Indians with different degrees of glucose intolerance. Their results showed that circulating levels of 1,5-AG became progressively lower as glucose intolerance increased, with individuals with NGT having the highest levels followed by those with IGR and DM, which is consistent with the findings in the present study. The serum 1,5-AG levels also have been suggested to be closely associated with diabetic retinopathy and cardiovascular diseases [18–20]. Thus, the 1,5-AG levels may be useful for identifying individuals at higher risk of
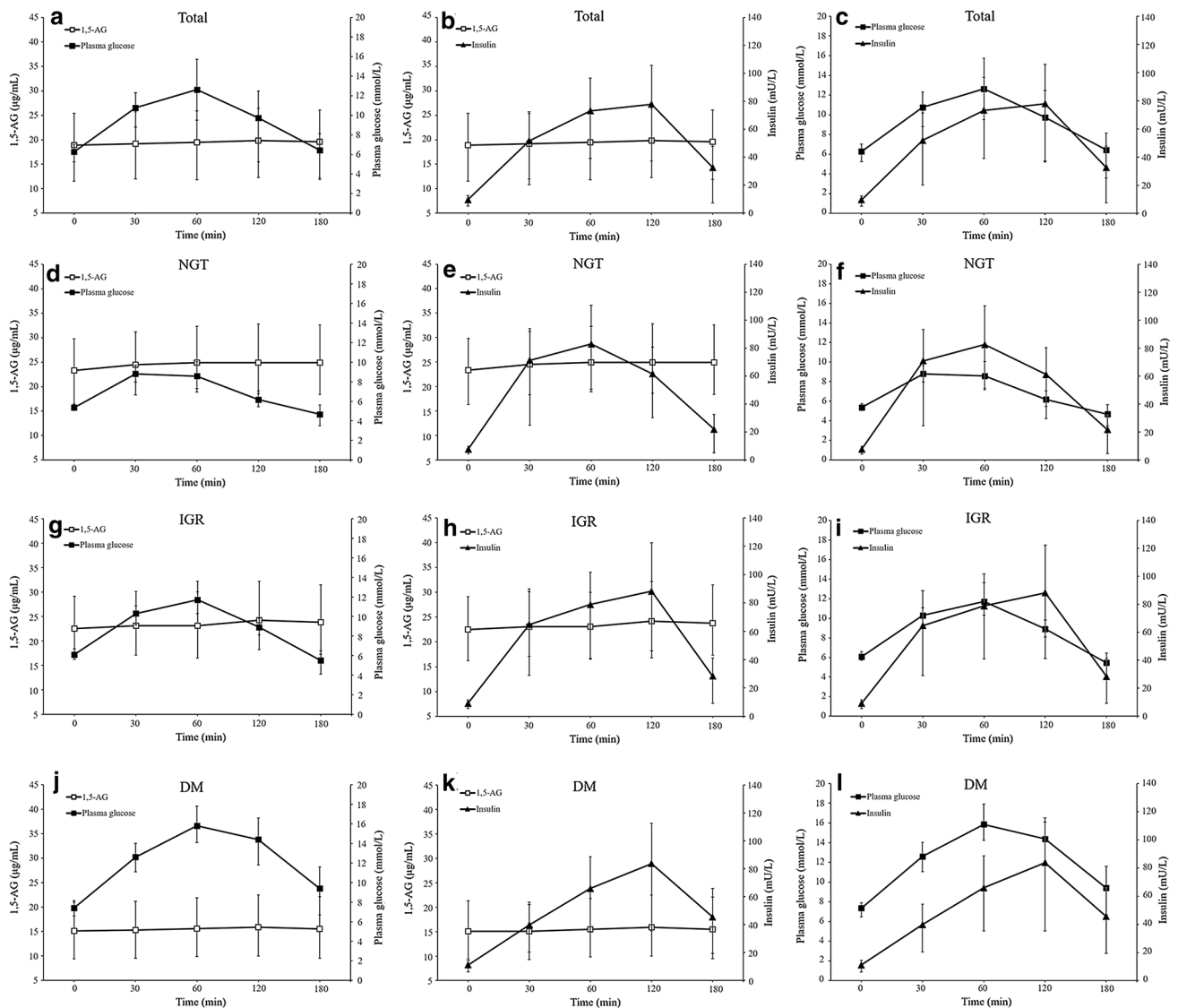
Fig. 1 Serum 1,5-AG, plasma glucose, and serum insulin levels of the entire study population (a–c) and of subgroups of participants divided according to differing degrees of glucose tolerance (NGT, d–f; IGR, g–i; DM, j–l). Data are expressed as median with interquartile ranges

these conditions [21–25]. Furthermore, in vitro studies have shown that 1,5-AG may regulate hepatic glucose metabolism by affecting both the glycogenolysis and gluconeogenesis pathways [26] and play an important role in the regulation of glucose-mediated insulin secretion [27].

Notably, we found that the serum 1,5-AG levels increased slightly, instead of declining, with the increase in blood glucose levels after a glucose load test. To date, few studies have evaluated the acute changes in 1,5-AG levels after glucose loading. The study reported by Akanuma et al. [10] included 5 participants with NGT, 7 with IGR, and 5 with DM who underwent a 100-g OGTT. They

observed that the 1,5-AG levels remained stable after an acute glucose load. In addition, a study [11] involving 77 healthy Japanese men found no significant changes in 1,5-AG levels between baseline and either 30 min or 60 min after a 75-g glucose load, but they observed significant increases in 1,5-AG levels at 90, 120, and 180 min after glucose loading, which is somewhat consistent with the findings in the present study.

The mechanisms underlying the minor changes in 1,5-AG levels after an acute glucose load are unknown. Previous studies revealed a kinetic mass balance model for 1,5-AG among kidney, plasma, and tissue pools [28].

**Table 2** Multiple stepwise regression analysis of factors independently associated with variation ranges ($\Delta$) of postload 1,5-AG levels

| Independent variables | Standardized $\beta$ | $t$ | $P$ |
|---|---|---|---|
| Model 1 | | | |
| $PG_{120}$ | −0.261 | −6.727 | <0.001 |
| BMI | −0.109 | −2.896 | 0.004 |
| Age | 0.131 | 3.448 | 0.001 |
| Model 2 | | | |
| $PG_{120}$ | −0.254 | −6.559 | <0.001 |
| Body weight | −0.136 | −3.618 | <0.001 |
| Age | 0.121 | 3.185 | 0.002 |
| Model 3 | | | |
| Total | | | |
| $1,5\text{-}AG_0$ | 0.376 | 10.529 | <0.001 |
| Body weight | −0.119 | −3.332 | 0.001 |
| Non-DM | | | |
| $1,5\text{-}AG_0$ | 0.372 | 7.612 | <0.001 |
| Body weight | −0.109 | −2.241 | 0.026 |
| Age | 0.105 | 2.147 | 0.032 |
| DM | | | |
| $1,5\text{-}AG_0$ | 0.189 | 3.093 | 0.002 |
| Body weight | −0.142 | −2.617 | 0.009 |
| $PG_{120}$ | −0.148 | −2.506 | 0.013 |

Model 1: age, gender, BMI, $HbA_{1c}$, $PG_0$, $PG_{30}$, $PG_{60}$, $PG_{120}$, $PG_{180}$, $INS_0$

Model 2: age, gender, body weight, $HbA_{1c}$, $PG_0$, $PG_{30}$, $PG_{60}$, $PG_{120}$, $PG_{180}$, $INS_0$

Model 3: age, gender, body weight, $HbA_{1c}$, $PG_0$, $PG_{30}$, $PG_{60}$, $PG_{120}$, $PG_{180}$, $INS_0$, $1,5\text{-}AG_0$

$\Delta1,5\text{-}AG$, range of variation in postload 1,5-anhydroglucitol levels; $1,5\text{-}AG_0$, fasting 1,5-anhydroglucitol; BMI, body mass index; DM, diabetes mellitus; $HbA_{1c}$, glycated hemoglobin $A_{1c}$; $INS_0$, fasting insulin; $PG_0$, fasting plasma glucose; $PG_{30}$, 30-min postload plasma glucose; $PG_{60}$, 60-min postload plasma glucose; $PG_{120}$, 120-min postload plasma glucose; $PG_{180}$, 180-min postload plasma glucose

Studies also showed that a drastic efflux of 1,5-AG from all tissues into the blood can be induced by the acute hyperglycemia [29, 30]. Therefore, we speculated that with the transport of a large amount of glucose into cells upon glucose loading, 1,5-AG would move from the intracellular space to the extracellular space and thereby cause the increase in circulating 1,5-AG levels after an acute glucose load. Moreover, our study indicated that postload 1,5-AG excursions were predominately and independently related to the baseline 1,5-AG level, which might be explained by the scale of the 1,5-AG pool in the entire body. Further research is needed to determine whether a shared membrane transport system is responsible for the transport of 1,5-AG and glucose.

Notably, we also found that body weight was a negative independent factor affecting postload 1,5-AG excursions. The underlying mechanisms might relate to the volume of body fluid, which can be reflected by body weight. With equal amounts of transcellular 1,5-AG evenly distributed in the extracellular fluid, a greater volume of body fluid might correspond to a decrease in $\Delta1,5\text{-}AG$.

Because baseline 1,5-AG levels differed between individuals with and without DM, we further analyzed factors influencing postload 1,5-AG excursions in these two populations. Our results showed that in addition to body weight and $1,5\text{-}AG_0$ levels, $PG_{120}$ was a positive independent factor for postload 1,5-AG excursions only in DM patients, and age was a negative independent factor for postload 1,5-AG excursions only in those without DM. The $PG_{120}$ can reflect circulating glucose concentrations, and an increasing trend could indicate a decreasing trend in the amount of glucose transported into cells under an equivalent glucose load (75 g) and a corresponding downtrend in the amount of 1,5-AG transported out of cells. In contrast, in individuals without DM, because of the relatively narrow range of postprandial blood glucose fluctuations, the impact of $PG_{120}$ on $\Delta1,5\text{-}AG$ was not obvious. The mechanism responsible for the effect of age on the $\Delta1,5\text{-}AG$ in participants without DM is not clear. Age might affect the $\Delta1,5\text{-}AG$ via a decline in the stability of the cell membrane, which could mean that more time is required to restore the balance of intracellular and extracellular 1,5-AG levels.

The present study indicated the serum 1,5-AG levels were slightly elevated by 6–7% rather than reduced after a glucose load, and no differences were found among participants of different gender, glucose metabolism status, or BMI, which suggests that it is reasonable to choose non-fasting 1,5-AG measurements for clinical use.

There are some limitations to this study. First, glycemic variability was only evaluated within a period of 180 min after administration of a 75-g glucose load. A longer observation period would provide a more complete picture of the changes in serum 1,5-AG levels. Second, the present study explored acute changes in 1,5-AG levels after only a 75-g glucose load. Moreover, further studies are needed to explore changes in 1,5-AG levels after an acute glucose load in individuals on different diets.

In conclusion, the present study demonstrated that, unlike the change associated with long-term hyperglycemia, the serum 1,5-AG levels were slightly elevated by 6–7% rather than reduced after a glucose load, and the results provided the first evidence that the baseline 1,5-AG level and body weight were independent and positive factors associated with the variation of postload 1,5-AG
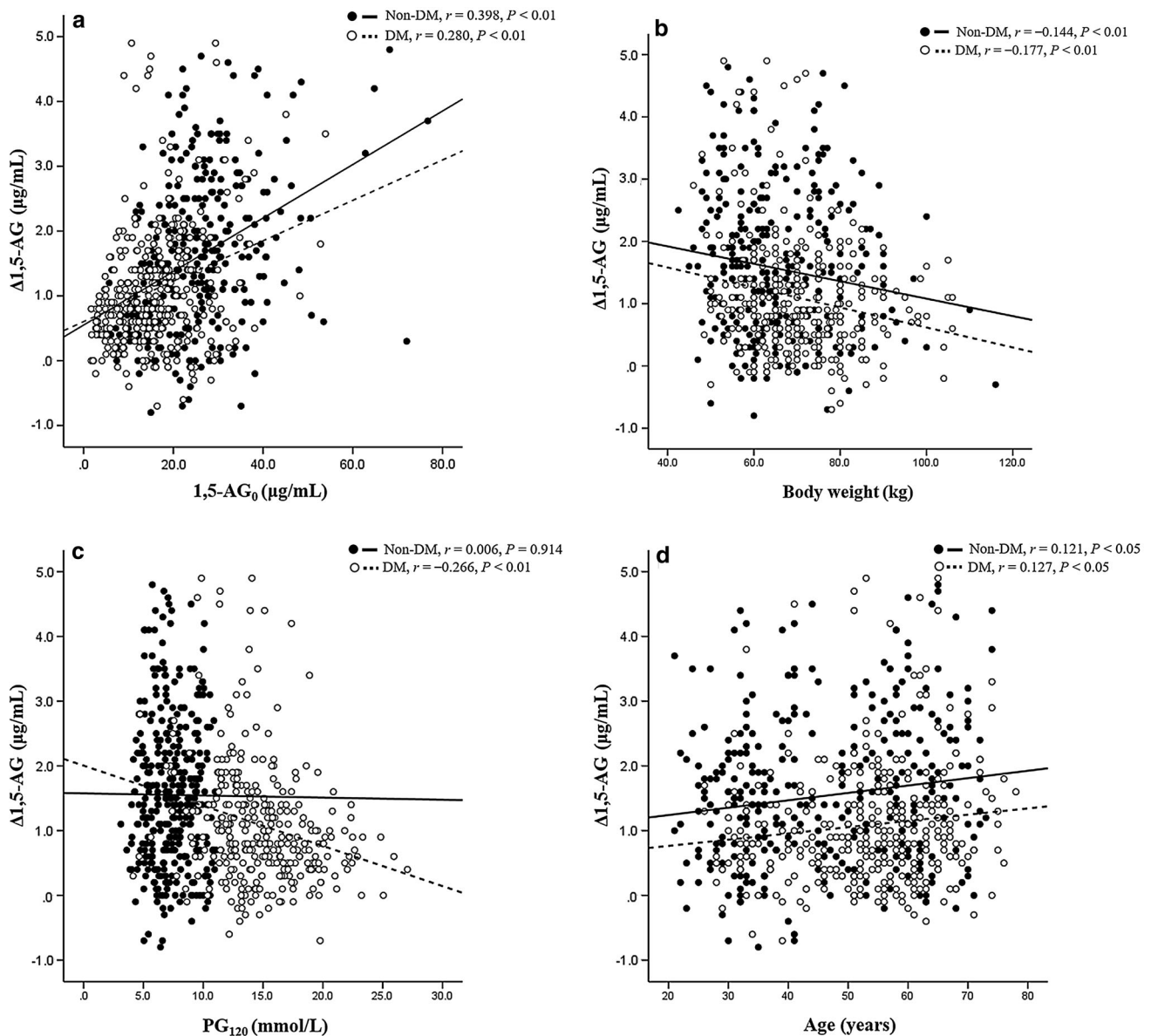
**Fig. 2** Associations of ranges of variation ($\Delta$) in postload 1,5-AG levels with **a** baseline 1,5-AG levels (1,5-AG$_0$), **b** body weight, **c** postload 120-min plasma glucose levels (PG$_{120}$), and **d** age in the DM group and non-DM group

levels. Because the mechanism for this change remains unclear, further studies in different 1,5-AG transport models are needed to investigate the relevant metabolic pathways.

revised the paper and contributed to the discussion. All authors read and approved the final manuscript.

**Compliance with ethical standards**

**Conflict of interest** The authors have nothing to disclose.

**Ethical disclosure** All procedures performed in studies involving human participants were in accordance with the ethical standards of the Ethics Committee of Shanghai Jiao Tong University Affiliated Sixth People's Hospital and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards.

**Human and animal rights** All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008.

**Informed consent** Informed consent was obtained from all individual participants included in the study.

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