Endocrine Journal 2011, **58** (1), 13-17

ORIGINAL

Correlation between baseline serum 1,5-anhydroglucitol levels and 2-hour post-challenge glucose levels during oral glucose tolerance tests

Maki Goto[1), 2)], Ritsuko Yamamoto-Honda[1)], Takuro Shimbo[3)], Atsushi Goto[1), 2)], Yasuo Terauchi[2)], Yasunori Kanazawa[4)] and Mitsuhiko Noda[1)]

[1)] *Department of Diabetes and Metabolic Medicine, National Center for Global Health and Medicine, Tokyo 162-8655, Japan*
[2)] *Department of Endocrinology and Metabolism, Yokohama City University Graduate School of Medicine, Yokohama 236-0004, Japan*
[3)] *Department of Clinical Research and Informatics, National Center for Global Health and Medicine, Tokyo 162-8655, Japan*
[4)] *Japan Diabetes Foundation, Tokyo 113-0033, Japan*

Abstract. Since there is increasing evidence that postprandial hyperglycemia is a risk factor for the development of macrovascular complications, it is important to predict postprandial hyperglycemia in the early stages of glucose intolerance, and routine medical checkups provide a good opportunity to do so. The aim of this study was to evaluate the usability of 1,5-anhydroglucitol (1,5-AG) in routine medical checkups. The subjects were 77 Japanese men who participated in a routine medical checkup. First, we performed 75 g oral glucose tolerance tests (OGTTs), and examined the changes in glucose and 1,5-AG levels measured at 0, 30, 60, 90, 120, and 180 minutes (min). 1,5-AG levels did not significantly change until 90 min after the glucose load. Second, a linear regression analysis showed an inverse correlation between the 2-hour post-challenge glucose (2h-PG) and baseline 1,5-AG levels during the OGTT ($P = 0.001$, $r^2 = 0.13$), and the correlation was still significant after adjustment for age (2h-PG = 170 + 0.83 × (age in years) - 3.23 × (1,5-AG), $P = 0.002$, adjusted $r^2 = 0.12$). Finally, to investigate the test characteristics of 1,5-AG levels as a predictor of a 2h-PG level ≥200 mg/dL, we plotted a receiver operating characteristic (ROC) curve. The area under the ROC curve was 0.78, and the maximal sum of sensitivity and specificity (78% and 72%, respectively) was obtained at a 1,5-AG cutoff level of <14.2 μg/mL. We conclude that 1,5-AG values may provide an ancillary predictor of 2h-PG of 75 g OGTTs in routine medical checkups.

Key words: 1,5-Anhydroglucitol, 75 g oral glucose tolerance test, Hyperglycemia

THE RESULTS of recent studies indicate that postprandial hyperglycemia may be an independent risk factor for the development of macrovascular complications [1, 2]. Although tight glycemic control is important to prevent complications of diabetes [3-5], many patients who are well controlled based on their HbA1c values have post-challenge hyperglycemia in oral glucose tolerance tests (OGTTs) [6]. 1,5-Anhydroglucitol (1,5-AG), a major 6-carbon dietary monosaccharide, is thought to reflect daily glycemic excursions, especially in patients whose HbA1c levels are at or near the goal [7, 8], and 1,5-AG levels have been reported to reflect postprandial glucose values in diabetic patients [9, 10]. 1,5-AG levels are also considered a useful indicator of glycemic control, because they correlate with fasting plasma glucose and HbA1c levels [11, 12], and they have been suggested to be a predictor of microvascular complications, such as diabetic retinopathy [13]. However, few studies have evaluated the change of 1,5-AG levels during OGTTs, or associations between baseline 1,5-AG levels and post-challenge glucose levels during OGTTs [14, 15]. Since it is important to predict postprandial hyperglycemia in the early stages of glucose intolerance, we thought routine medical checkups would provide a good opportunity to do so. Therefore, in the present study we assessed the usability of the 1,5-AG levels

Received Jul. 23, 2010; Accepted Oct. 15, 2010 as K10E-224
Released online in J-STAGE as advance publication Nov. 12, 2010
Correspondence to: Mitsuhiko Noda, Department of Diabetes and Metabolic Medicine, National Center for Global Health and Medicine, 1-21-1 Toyama, Shinjuku-ku, Tokyo 162-8655, Japan.
E-mail: mnoda@hosp.ncgm.go.jp

by using the data obtained during the OGTTs of participants in a routine medical checkup.

First, to assess whether 1,5-AG levels depend on fasting states, we examined the changes in serum 1,5-AG levels during OGTTs. Second, to assess baseline 1,5-AG levels as a predictor of post-challenge hyperglycemia, we examined the relations between the baseline 1,5-AG levels and 2-hour post-challenge glucose (2h-PG) levels after the glucose load. 2h-PG levels have been found to be more strongly associated with atherosclerosis than fasting plasma glucose or maximal post-challenge glucose levels have [1]. Finally, to investigate the test characteristics of the 1,5-AG levels as a predictor of a 2h-PG level ≥200 mg/dL, we plotted a receiver operating characteristic (ROC) curve and determined the optimal cutoff level. A casual plasma glucose level ≥200 mg/dL is the threshold for the diagnosis of diabetes, and the incidences of ischemic stroke in both sexes and of coronary heart disease in women have been found to be significantly higher in Japanese with a 2-hour OGTT glucose level ≥200 mg/dL [16].

Subjects and Methods

Subjects

The subjects were 77 male Japanese office workers who received routine medical checkups in 1988. The data were untraceable and anonymous. Participants in the checkups who were being treated with oral hypoglycemic agents or insulin were excluded.

Methods

Subjects ingested a 75 g glucose load (Trelan-G75, Shimizu Pharmaceutical, Shimizu, Japan) after an overnight fast. Venous blood samples were collected at 0 minutes (min), 30 min , 60 min, 90 min, 120 min, and 180 min after ingestion of the glucose load, and the serum 1,5-AG concentration and plasma glucose concentration in each sample were measured.

Measurements

Serum 1,5-AG concentrations were determined by a column enzymatic method that used pyranose oxidase (Nippon Kayaku, Tokyo, Japan). The inter-assay coefficient of variation has been reported to be <5% [12, 17].

Statistical analysis

First, a repeated measures analysis of variance (ANOVA) was used to analyze the changes in serum 1,5-AG and plasma glucose levels after the glucose load in the OGTT. Second, a linear regression model was used to regress the 2h-PG against the baseline 1,5-AG values. Because 1,5-AG levels have been reported to vary with age [14], we performed the linear regression with adjustment for age. Finally, to investigate the test characteristics of the 1,5-AG levels as a predictor of a 2h-PG level ≥200 mg/dL, we plotted a receiver operating characteristic (ROC) curve. The significance level was defined as $\alpha = 0.05$. The statistical analysis was performed by using the STATA 11.0 software program.

Results

The age of the subjects was 49.7 ± 7.9 years (mean ± SD). According to the results of the OGTTs, there were 37 subjects with normal glucose tolerance, 4 with impaired fasting glycemia (IFG), 12 with impaired glucose tolerance (IGT), 4 with IFG/IGT, and 20 with diabetes. Normal glucose tolerance, IFG, IGT, and diabetes were diagnosed according to the World Health Organization Criteria [18]. Glycated hemoglobin and body mass index data were unavailable.

The changes in plasma glucose and serum 1,5-AG levels during the OGTT are shown in Table 1. The mean fasting plasma glucose level was 107.5 ± 16.5 mg/dL, and the mean 2h-PG level was 156.8 ± 66.2 mg/dL.

Serum 1,5-AG levels after the glucose load during the OGTTs

The differences between the 1,5-AG levels at 0 min, 30 min, 60 min, 90 min, 120 min, and 180 min were analyzed by ANOVA. There were no significant changes in 1,5-AG levels between the baseline and either 30 min or 60 min, but there were significant increases at 90 min, 120 min, and 180 min (Table 1).

Correlation between 2h-PG levels and 1,5-AG levels

The results of the linear regression analysis showed an inverse correlation between the 1,5-AG levels and the 2h-PG levels in the OGTTs (Fig. 1). The regression coefficient (SE) of 1,5-AG was -3.42 (1.01), and 2h-PG was calculated by using the formula: 2h-PG = 214 - 3.42 × (1,5-AG) ($P = 0.001$, $r^2 = 0.13$). The correlation was still significant after adjustment for age. The regression coefficients of age and the 1,5-AG lev-

Table 1 Plasma glucose and serum 1,5-AG levels during oral glucose tolerance tests (OGTTs) .

	0 min	30 min	60 min	90 min	120 min	180 min
Glucose (mg/dL)	107.5 ± 16.5	191.4 ± 38.7*	217.6 ± 53.0*	188.0 ± 62.3*	156.8 ± 66.2*	97.9 ± 52.1
1,5-AG (μg/mL)	16.7 ± 7.0	16.5 ± 7.1	16.7 ± 7.1	17.1 ± 7.4*	17.3 ± 7.4*	17.1 ± 7.3*

Data are means ± SD. * Significant difference from the level at 0 min (ANOVA). Using Bonferroni adjustment for multiple testing, $P < 0.01$ were considered significant.

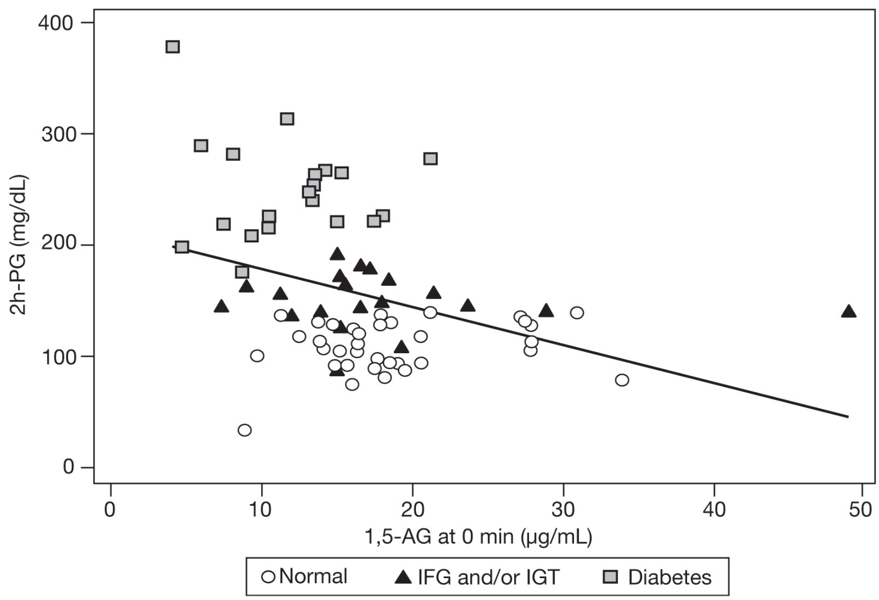

Fig. 1 Correlation between 2h-PG and 1,5-AG levels. The solid line is the fitted regression line. The regression coefficient (SE) of 1,5-AG was - 3.42 (1.01), and the 2h-PG level was calculated by the formula: 2h-PG = 214 - 3.42 × (1,5-AG) (P = 0.001, r^2 = 0.13).

els were: age 0.83 (0.92) and 1,5-AG -3.23 (1.03). The 2h-PG level was calculated, thus: 2h-PG = 170 + 0.83 × (age in years) - 3.23 × (1,5-AG), P = 0.002, adjusted r^2 = 0.12. However, the correlation did not remain significant after adjusting for the fasting plasma glucose levels.

ROC curve

The area under the ROC curve was 0.78 (95% confidence interval: 0.67 to 0.87). The maximal sum of sensitivity and specificity (78% and 72%, respectively) was obtained at a 1,5-AG cutoff level of <14.2 μg/mL (Fig. 2).

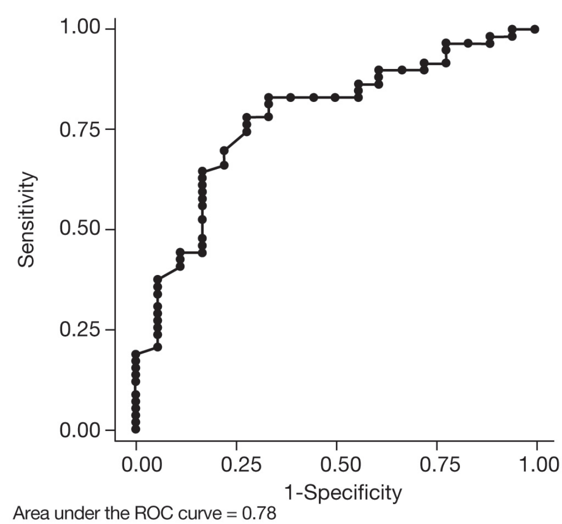

Fig. 2 ROC curve for the ability of the 1,5-AG level to predict a 2h-PG level ≥200 mg/dL. The maximal sum of sensitivity and specificity (78% and 72%, respectively) was obtained at a 1,5-AG cutoff level of <14.2 μg/mL.

Discussion

The 1,5-AG levels of participants in routine medical checkups may provide an ancillary predictor of post-challenge hyperglycemia. The unique aspect of this study is that the values were obtained during routine medical checkups of Japanese office workers. Their mean fasting plasma glucose level was 107.5 mg/dL, and this population included not only participants with normal glycemia, but also participants with IGT, IFG, and diabetes. The results of the linear regression analysis showed a correlation between their 2h-PG levels in OGTTs and baseline serum 1,5-AG levels.

In view of the risk of 2-hour post-challenge hyperglycemia, we also presumed to use a 1,5-AG cutoff level of <14.2 μg/mL to screen for 2-hour post-challenge hyperglycemia, and its sensitivity and specificity for a 2h-PG level ≥200 mg/dL in the OGTT at the cutoff level were 78% and 72%, respectively. This is consistent with the 1,5-AG cutoff level used for diagnosing diabetes in previous studies in Japanese [12, 14].

We measured serum 1,5-AG during the OGTTs, and the data may be useful for evaluating the dynamics of 1,5-AG. In a preceding study in Japan, the increase of 1,5-AG measured by hours during OGTT has been reported [15]. In our study, there were no significant changes in 1,5-AG levels between the baseline and either 30 min or 60 min, but there were significant increases at 90 min, 120 min, and 180 min. The mechanism responsible for the increases may be the movement of 1,5-AG from the intracellular space to the extracellular space after a glycemic load, and a membrane transport system has been hypothesized [19-23]. When 1,5-AG is measured during routine checkups, fasting 1,5-AG is recommended, but our findings suggest that the increase in 1,5-AG after a glucose load is clinically negligible.

The limitations of our study were the small sample size, the limited generalizability, the subjects all being men, and the inability to compare the 1,5-AG levels with HbA1c values. However, a recent study has shown that 1,5-AG levels reflect glycemic excursions more robustly than HbA1c values do in patients with moderately controlled diabetes [24], and there were no differences between 1,5-AG cutoff levels according to gender [12, 14]. Also, 1,5-AG levels are affected by diet, which differs significantly from country to country, and differences between absolute 1,5-AG levels in Asians and Caucasians have been reported [25]. If 1,5-AG is used as a predictor of post-challenge hyperglycemia, it will be important to select cutoff levels that are appropriate for the subjects in each region, and prospective studies with a large sample size will be necessary to confirm 1,5-AG as a predictor of future atherosclerosis.

To summarize, the results of this study revealed a correlation between serum 1,5-AG levels and the 2h-PG levels during OGTTs, and the correlation was still significant after adjustment for age. We conclude that 1,5-AG values may provide an ancillary predictor of 2h-PG of 75 g OGTTs in participants in routine medical checkups.

References

1. Temelkova-Kurktschiev TS, Koehler C, Henkel E, Leonhardt W, Fuecker K, Hanefeld M (2000) Postchallenge plasma glucose and glycemic spikes are more strongly associated with atherosclerosis than fasting glucose or HbA1c level. *Diabetes Care* 23: 1830-1834.
2. Hanefeld M, Fischer S, Julius U, Schulze J, Schwanebeck U, Schmechel H, Ziegelasch HJ, Lindner J (1996) Risk factors for myocardial infarction and death in newly detected NIDDM: the Diabetes Intervention Study, 11-year follow-up. *Diabetologia* 39: 1577-1583.
3. The Diabetes Control and Complications Trial Research Group (1993) The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. The Diabetes Control and Complications Trial Research Group. *N Engl J Med* 329: 977-986.
4. UK Prospective Diabetes Study (UKPDS) Group (1998) Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). UK Prospective Diabetes Study (UKPDS) Group. *Lancet* 352: 837-853.
5. UKPDS Group (1998) Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). UK Prospective Diabetes Study (UKPDS) Group. *Lancet* 352: 854-865.
6. Erlinger TP, Brancati FL (2001) Postchallenge hyperglycemia in a national sample of U.S. adults with type 2 diabetes. *Diabetes Care* 24: 1734-1738.
7. Kishimoto M, Yamasaki Y, Kubota M, Arai K, Morishima T, Kawamori R, Kamada T (1995) 1,5-Anhydro-D-glucitol evaluates daily glycemic excursions in well-controlled NIDDM. *Diabetes Care* 18: 1156-1159.

8. Yamanouchi T, Inoue T, Ogata E, Kashiwabara A, Ogata N, Sekino N, Yoshimura T, Ichiyanagi K, Kawasaki T (2001) Post-load glucose measurements in oral glucose tolerance tests correlate well with 1,5-anhydroglucitol, an indicator of overall glycaemic state, in subjects with impaired glucose tolerance. *Clin Sci (Lond)* 101: 227-233.
9. Stettler C, Stahl M, Allemann S, Diem P, Schmidlin K, Zwahlen M, Riesen W, Keller U, Christ E (2008) Association of 1,5-anhydroglucitol and 2-h postprandial blood glucose in type 2 diabetic patients. *Diabetes Care* 31: 1534-1535.
10. Won JC, Park CY, Park HS, Kim JH, Choi ES, Rhee EJ, Lee WY, Oh KW, Kim SW, Park SW (2009) 1,5-Anhydroglucitol reflects postprandial hyperglycemia and a decreased insulinogenic index, even in subjects with prediabetes and well-controlled type 2 diabetes. *Diabetes Res Clin Pract* 84: 51-57.
11. Yamanouchi T, Minoda S, Yabuuchi M, Akanuma Y, Akanuma H, Miyashita H, Akaoka I (1989) Plasma 1,5-anhydro-D-glucitol as new clinical marker of glycemic control in NIDDM patients. *Diabetes* 38: 723-729.
12. Yamanouchi T, Akanuma Y, Toyota T, Kuzuya T, Kawai T, Kawazu S, Yoshioka S, Kanazawa Y, Ohta M, Baba S, et al. (1991) Comparison of 1,5-anhydroglucitol, HbA1c, and fructosamine for detection of diabetes mellitus. *Diabetes* 40: 52-57.
13. Hoshino K, Akanuma Y (2004) Relationship between 1,5-anhydroglucitol and development of diabetic retinopathy. *J Jpn Diab Soc* 47: 845-850 (In Japanese).
14. Yamanouchi T, Akanuma Y, Toyota T, Kuzuya T, Kawai T, Kawazu S, Yoshioka S, Kanazawa Y, Ohta M, Baba S, Kosaka K (1990) Clinical significance of serum 1,5-anhydroglucitol measurements in diabetes mellitus. *J Jpn Diab Soc* 33: 41-48 (In Japanese).
15. Yoshioka N, Nakatsu T, Fukuzawa N, Akanuma Y (1993) Changes in plasma and urinary concentrations of 1,5-Anhydro-D-Glucitol during oral glucose tolerance test. *J Jpn Diab Soc* 36: 839-845 (In Japanese).
16. Doi Y, Ninomiya T, Hata J, Fukuhara M, Yonemoto K, Iwase M, Iida M, Kiyohara Y (2010) Impact of glucose tolerance status on development of ischemic stroke and coronary heart disease in a general Japanese population: the Hisayama study. *Stroke* 41: 203-209.
17. Yabuuchi M, Masuda M, Katoh K, Nakamura T, Akanuma H (1989) Simple enzymatic method for determining 1,5-anhydro-D-glucitol in plasma for diagnosis of diabetes mellitus. *Clin Chem* 35: 2039-2043.
18. Alberti KG, Zimmet PZ (1998) Definition, diagnosis and classification of diabetes mellitus and its complications. Part 1: diagnosis and classification of diabetes mellitus provisional report of a WHO consultation. *Diabet Med* 15: 539-553.
19. Okuno Y, Nishizawa Y, Kawagishi T, Sekiya K, Shoji T, Morii H (1992) Transport of 1,5-anhydro-D-glucitol into human polymorphonuclear leukocytes. *J Biochem* 111: 99-102.
20. Suzuki M, Akanuma H, Akanuma Y (1988) Transport of 1,5-anhydro-D-glucitol across plasma membranes in rat hepatoma cells. *J Biochem* 104: 956-959.
21. Yamanouchi T, Ogata N, Yoshimura T, Inoue T, Ogata E, Kawasaki T, Kashiwabara A, Muraoka H (2000) Transport of 1,5-anhydro-D-glucitol into insulinoma cells by a glucose-sensitive transport system. *Biochim Biophys Acta* 1474: 291-298.
22. Yamanouchi T, Tachibana Y, Akanuma H, Minoda S, Shinohara T, Moromizato H, Miyashita H, Akaoka I (1992) Origin and disposal of 1,5-anhydroglucitol, a major polyol in the human body. *Am J Physiol* 263: E268-273.
23. Yamanouchi T, Tachibana Y, Sekino N, Akanuma H, Akaoka I, Miyashita H (1994) Transport and accumulation of 1,5-anhydro-D-glucitol in the human erythroleukemia cell line K-562. *J Biol Chem* 269: 9664-9668.
24. Dungan KM, Buse JB, Largay J, Kelly MM, Button EA, Kato S, Wittlin S (2006) 1,5-anhydroglucitol and postprandial hyperglycemia as measured by continuous glucose monitoring system in moderately controlled patients with diabetes. *Diabetes Care* 29: 1214-1219.
25. Herman WH, Dungan KM, Wolffenbuttel BH, Buse JB, Fahrbach JL, Jiang H, Martin S (2009) Racial and ethnic differences in mean plasma glucose, hemoglobin A1c, and 1,5-anhydroglucitol in over 2000 patients with type 2 diabetes. *J Clin Endocrinol Metab* 94: 1689-1694.