ORIGINAL ARTICLE

Increased 1,5-Anhydroglucitol Predicts Glycemic Remission in Patients with Newly Diagnosed Type 2 Diabetes Treated with Short-Term Intensive Insulin Therapy

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Abstract

Background: Short-term intensive insulin therapy has been shown to induce long-term glycemic remission in patients with newly diagnosed type 2 diabetes. However, predictors of remission are still uncertain. This study was conducted to evaluate whether changes of 1,5-anhydroglucitol (1,5AG) and fructosamine (FA) could be a predictor of remission.

Subjects and Methods: Newly diagnosed drug-naïve patients with type 2 diabetes ($n=64$) were enrolled. After baseline assessments, continuous subcutaneous insulin infusion (CSII) was administered in all patients until euglycemia was achieved and maintained for another 2 weeks. Patients were subsequently followed monthly for 3 months. 1,5AG and FA were measured before and after therapy and at 1-month follow-up.

Results: After CSII, A1C and FA decreased from baseline, whereas 1,5AG increased. 1,5AG was higher at 1-month follow-up (11.5 ± 4.1 vs. 6.7 ± 2.8 mg/L, $P < 0.001$), whereas FA was lower (273.1 ± 56.1 vs. 316.2 ± 39.3 μ mol/L, $P = 0.021$) in the remission group. Stepwise logistic regression analysis showed that 1,5AG at 1-month follow-up rather than FA was an independent predictor of remission after adjusting for other confounders (odds ratio 1.56, 95% confidence interval [CI] 1.15–2.12, $P = 0.004$). The area under the curve of the receiver operating characteristic curve analysis was 0.85 (95% CI 0.75–0.96, $P < 0.001$). The optimal cutoff point for 1,5AG at 1-month follow-up was 8.9 mg/L (specificity, 83.3%; sensitivity, 78.6%).

Conclusions: Improvement of 1,5AG predicts maintenance of glycemic remission after intensive insulin therapy in patients with newly diagnosed type 2 diabetes.

Introduction

PREVIOUS STUDIES SHOWED that short-term intensive insulin therapy in patients with newly diagnosed type 2 diabetes mellitus could induce long-term drug-free glycemic remission.^{1–3} In our multicenter, randomized, parallel-group trial, the 1-year remission rate was significantly greater in the short-term continuous subcutaneous insulin infusion (CSII) group (51.1%) compared with the oral hypoglycemic agents group (26.7%).² Improvement of β -cell function, especially restoration of the acute insulin response (AIR) measured by the intravenous glucose tolerance test (IVGTT), was the main predictive factor for glycemic remission. However, more convenient indicators of glycemic remission, particularly glycemic predictors that can be used in practice, are yet to be found.

1,5-Anhydroglucitol (1,5AG) is a sensitive glycemic marker that reflects short-term glycemic changes.^{4,5} We conducted this study to determine whether 1,5AG was an effective pre-

dictor of glycemic remission after short-term insulin therapy in patients with newly diagnosed type 2 diabetes.

Subjects and Methods

Subjects

Between June 2008 and May 2010, we recruited patients between 25 and 70 years old who were newly diagnosed with type 2 diabetes according to the World Health Organization 1999 criteria. Fasting plasma glucose (FPG) of the subjects ranged between 7.0 to 16.7 mmol/L. No patients had received any antihyperglycemic agents prior to the recruitment. Exclusion criteria included acute or severe chronic diabetes complications, severe concomitant diseases, or use of medications affecting glucose metabolism. Written informed consent was obtained from each participant. The protocol and informed consent document were approved by the Research Ethics Board of Sun Yat-Sen University.

Study design and measurements

All patients were admitted to the hospital upon diagnosis and guided to start lifestyle intervention. After measurement of anthropometric indices, fasting blood samples were collected for FPG, glycated hemoglobin A_{1c} (A1C), 1,5AG, and fructosamine (FA) assessments. An IVGTT was then performed in each subject as described previously using 25 g of glucose (50 mL of 50% glucose).² Blood samples were collected before and 1, 2, 4, 6, and 10 min after glucose infusion for insulin measurements. The 2-h postprandial plasma glucose (2hPG) was measured after breakfast on the day after the IVGTT was performed. After baseline assessments, intensive insulin therapy using insulin aspart (NovoRapid®; Novo Nordisk, Bagsværd, Denmark) was administered to all patients with an insulin pump (Paradigm 712 pump, Medtronic, Inc., Northridge, CA). Initial insulin doses were 0.5–0.6 international units (IU)/kg with total daily doses divided 50:50 for basal and bolus infusion. Dosages of insulin were titrated to achieve glycemic targets (4.4–6.0 mmol/L and 4.4–7.8 mmol/L for fasting and 2-h postprandial capillary blood glucose, respectively). Euglycemia was maintained for another 2 weeks. Thereafter, CSII was stopped. Measurements of FPG, 1,5AG, FA, A1C, and IVGTT were repeated the next day, which was at least 15 h after the cessation of insulin infusion. The 2hPG after breakfast was measured the day after the IVGTT.

After discharge from the hospital, patients were encouraged to maintain diet control and exercise as initially instructed to maintain optimum glycemic control, which was defined as FPG <7.0 mmol/L and 2hPG <10 mmol/L. Patients were followed up monthly for 3 months with FPG and 2hPG measured in each follow-up. All patients remained off antihyperglycemic agents until the 1-month follow-up, when 1,5AG and FA were measured. Thereafter, patients with glycemic relapse were confirmed by a repeat plasma examination 1 week later. Then antihyperglycemic therapy was started according to current Chinese diabetes guidelines. Patients who maintained optimum glycemic control for at least 3 months without medication were defined as the remission group, and those with hyperglycemic relapse were defined as the non-remission group.

Enzymatic colorimetric assays were used to measure serum 1,5AG (Kyowa Medek Co., Ltd., Tokyo, Japan) and FA (GlyPro reagent; Genzyme Diagnostic Co., Oxford, UK) levels. A1C was measured using high-performance liquid chromatography (Bio-Rad Laboratories, Hercules, CA). All assays were done in the central laboratory of the First Affiliated Hospital of Sun Yat-Sen University.

Homeostasis model assessment was used to measure β -cell function (HOMA-B) and insulin resistance (HOMA-IR) at each time point using the following equations: HOMA-B = $20 \times \text{fasting insulin} / (\text{FPG} - 3.5)$ and HOMA-IR = $(\text{FPG} \times \text{fasting insulin}) / 22.5$. AIR was calculated as the incremental trapezoidal area during the first 10 min after glucose administration in the IVGTT.

Statistical analysis

Normally distributed data are presented as mean $\pm$ SD values, and nonnormally distributed data are presented as median (interquartile range, 25–75%). Before and after treatment differences were assessed with paired Student's *t* test

(normally distributed data) or Wilcoxon test (nonnormally distributed data). Differences between groups were assessed with an independent *t* test (normally distributed data) or the Mann–Whitney test (nonnormally distributed data). Correlations between glycemic markers and log transformed AIR after CSII (log AIR) were evaluated with partial correlation. A stepwise logistic regression was used to estimate the risk factors of remission. Variables were included in the model if $P < 0.05$ and removed if $P > 0.1$. Receiver operating characteristic curve analysis was performed to estimate the predictive effect of 1,5AG. The optimal cutoff point of 1,5AG was decided as the value with the highest Youden index, which is calculated as sensitivity plus specificity – 1.⁶ Statistical analyses were performed with SPSS version 13.0 software (SPSS, Inc., Chicago, IL).

Results

Patients (44 men and 20 women) were 49.3 ± 9.6 years of age with a body mass index of 25.5 ± 3.4 kg/m². All patients achieved glycemic targets within 1 week without a severe hypoglycemia episode. After CSII, glycemic markers such as FPG, 2hPG, A1C, FA, and 1,5AG were all ameliorated significantly compared with baseline values. The percentage of change from baseline of 1,5AG, FA, and A1C were 221.7% (229.3%), –36.5% (13.8%), and –13.0% (6.1%), respectively. Both HOMA-B and AIR increased significantly, whereas HOMA-IR decreased (Table 1). After adjusting for age and body mass index, both 1,5AG ($r = 0.28$, $P = 0.033$) and FA ($r = -0.32$, $P = 0.03$) after CSII correlated with log AIR after CSII, but A1C showed no significant correlation with log AIR.

Forty-two subjects (32 men and 10 women) of the 64 patients (66%) remained in remission during follow-up. Baseline clinical characteristics between the remission and non-remission groups were comparable. Daily insulin

TABLE 1. COMPARISON OF GLYCEMIC CONTROL AND β -CELL FUNCTION BEFORE AND AFTER CONTINUOUS SUBCUTANEOUS INSULIN INFUSION

	Before CSII	After CSII ^a	P
FPG (mmol/L)	11.9 $\pm$ 3.0	6.6 $\pm$ 1.7	<0.001
2hPG (mmol/L)	17.8 $\pm$ 5.7	8.7 $\pm$ 3.1	<0.001
A1C (%)	11.1 $\pm$ 1.8	9.6 $\pm$ 1.4	<0.001
FA (μ mol/L)	538.9 $\pm$ 167.5	332.3 $\pm$ 83.8	<0.001
1,5AG (mg/L)	2.8 $\pm$ 2.9	7.9 $\pm$ 3.8	<0.001
HOMA-B	17.6 (19.2)	55.9 (44.3)	<0.001
AIR (mIU/L/min)	–11.1 (21.9)	53.7 (89.5)	<0.001
HOMA-IR	3.7 (2.1)	2.0 (1.1)	<0.001

Data are mean $\pm$ SD values or median (interquartile range, 25–75%) as indicated.

^aFasting plasma glucose (FPG), 1,5-anhydroglucitol (1,5AG), fructosamine (FA), glycated hemoglobin A_{1c} (A1C), and the intravenous glucose tolerance test were repeated as baseline on the next day, which was at least 15 h after cessation of insulin infusion. The 2-h postprandial plasma glucose (2hPG) was measured on the day after the intravenous glucose tolerance test, after breakfast.

AIR, acute insulin response; CSII, continuous subcutaneous insulin infusion; HOMA-B, homeostasis model assessment of β -cell function; HOMA-IR, homeostasis model assessment of insulin resistance.

requirements for achieving glycemic targets were also similar between the two groups (remission group, 0.78 ± 0.13 U/day; non-remission group, 0.84 ± 0.15 U/kg; $P=0.12$). The remission group had lower FPG and 2hPG values after CSII and at 1-month follow-up. After CSII was stopped, the improvement of HOMA-IR, HOMA-B, and AIR was better in the remission group. Significant differences of FA and 1,5AG levels between the two groups did not occur until at 1-month follow-up: 1,5AG was higher (11.5 ± 4.1 vs. 6.7 ± 2.8 mg/L; $P<0.001$), whereas FA was lower (273.1 ± 56.1 vs. 316.2 ± 39.3 μ mol/L; $P=0.021$) in the remission group (Table 2).

If differences in each variable between the two groups achieved a P value of <0.2 in Table 2, they were evaluated

TABLE 2. COMPARISON OF CLINICAL CHARACTERISTICS OF REMISSION AND NON-REMISSION GROUPS

	Remission (n=42)	Non-remission (n=22)	P
Age (years)	47.1 ± 8.5	53.6 ± 10.4	0.060
BMI (kg/m^2)	25.6 ± 3.2	25.4 ± 3.9	0.903
FPG (mmol/L)			
Before CSII	11.6 ± 3.2	12.3 ± 2.3	0.355
After CSII ^a	6.2 ± 1.4	7.5 ± 1.6	0.002 ^b
1-month follow-up	5.9 ± 0.8	7.3 ± 1.1	0.001 ^b
2hPG (mmol/L)			
Before CSII	17.2 ± 5.7	19.0 ± 5.4	0.287
After CSII ^a	7.5 ± 2.2	11.0 ± 3.3	0.001 ^b
1-month follow-up	7.5 ± 1.6	10.0 ± 1.7	0.001 ^b
A1C (%)			
Before CSII	11.0 ± 1.8	11.3 ± 1.7	0.557
After CSII ^a	9.4 ± 1.4	9.8 ± 1.4	0.314
FA (μ mol/L)			
Before CSII	532.5 ± 185.3	549.8 ± 130.2	0.699
After CSII ^a	325.1 ± 87.0	346.0 ± 77.5	0.348
1-month follow-up	273.1 ± 56.1	316.2 ± 39.3	0.021 ^b
1,5AG (mg/L)			
Before CSII	3.1 ± 3.5	2.1 ± 1.0	0.180
After CSII ^a	8.1 ± 4.1	7.4 ± 3.1	0.524
1-month follow-up	11.5 ± 4.1	6.7 ± 2.8	0.001 ^b
HOMA-IR			
Before CSII	3.7 (1.9)	4.3 (2.7)	0.493
After CSII ^a	1.9 (1.0)	2.3 (2.0)	0.031 ^b
HOMA-B			
Before CSII	17.8 (21.0)	15.4 (19.4)	0.109
After CSII ^a	63.1 (60.1)	52.2 (42.0)	0.026 ^b
AIR (mIU/L/min)			
Before CSII	-11.8 (24.9)	-8.8 (10.9)	0.373
After CSII ^a	67.1 (94.2)	26.9 (54.2)	0.003 ^b

Data are mean $\pm$ SD values or median (interquartile range, 25–75%) as indicated.

^aFasting plasma glucose (FPG), 1,5-anhydroglucitol (1,5AG), fructosamine (FA), glycated hemoglobin A_{1C} (A1C), and the intravenous glucose tolerance test were repeated on the next morning after suspension of the insulin pump, which was at least 15 h after the cessation of insulin infusion. The 2h-postprandial plasma glucose (2hPG) was measured on the day after the intravenous glucose tolerance test, after breakfast.

^b $P<0.05$ was a significant difference.

AIR, acute insulin response; BMI, body mass index; CSII, continuous subcutaneous insulin infusion; HOMA-B, homeostasis model assessment of β -cell function; HOMA-IR, homeostasis model assessment of insulin resistance.

TABLE 3. INDEPENDENT PREDICTORS OF REMISSION IN STEPWISE LOGISTIC REGRESSION

Variable	Odds ratio	95% CI	P
Age	0.84	0.72–0.98	0.027
1,5-Anhydroglucitol at 1-month follow-up	1.56	1.15–2.12	0.004
HOMA-IR after CSII	0.38	0.15–0.99	0.048

Other covariables that are not statistically significant are not shown here. These covariables include homeostasis model assessment of β -cell function after continuous subcutaneous insulin infusion (CSII), acute insulin response after CSII, fasting plasma glucose after CSII and at 1-month follow-up, 2-h postprandial plasma glucose after CSII and at 1-month follow-up, and fructosamine at 1-month follow-up.

CI, confidence interval; HOMA-IR, homeostasis model assessment of insulin resistance.

with stepwise logistic regression for identification of potential independent predictors of remission. In the final model, 1,5AG at 1-month follow-up was an independent predictor of remission (odds ratio 1.56, 95% confidence interval [CI] 1.15–2.12, $P=0.004$). Other predictors included age and HOMA-IR after CSII. The odds ratios of other variables were not statistically significant after adjusting for confounders (Table 3). The area under the curve of 1,5AG in the receiver operating characteristic curve analysis was 0.85 (95% CI 0.75–0.96, $P<0.001$), and the optimal cutoff point identified with the Youden index was 8.9 mg/L (specificity, 83.3%; sensitivity, 78.6%; positive predictive value, 94.3%; negative predictive value, 52.6%) (Fig. 1).

FIG. 1. Predictive effect of 1,5-anhydroglucitol at 1-month follow-up for glycemic remission. ROC, receiver operating characteristic.

Discussion

1,5-AG is a polyol that originates mostly from ingested foods; 99% of 1,5AG is reabsorbed in renal tubules to constantly maintain a body pool of about 500–1,000 mg. In the hyperglycemic state, when the glycosuric threshold is exceeded, reabsorption of 1,5AG is competitively inhibited, which leads to a rapid decrease of 1,5AG concentration.⁵ Therefore, 1,5AG is validated as a short-term glycemic marker reflecting glycemic control within the previous 2 weeks. Previous studies had shown that 1,5AG was more sensitive than A1C and FA in responding to modification of glycemic therapy in the short term.^{7,8} In this study, the 1,5AG level increased substantially after 2 weeks of intensive insulin therapy, which is in consistent with other studies.^{7,8} This implies that 1,5AG might be a sensitive glycemic marker in the situation of rapidly changing blood glucose level such as those achieved with short-term intensive insulin therapy in this study or, conversely, when glycemic control rapidly deteriorates.

The improvement of β -cell function and the induction of remission after tight glycemic control, which were shown in this study, are similar to our previous studies.^{1,2} The mechanisms contributing to glycemic remission, however, are not fully understood. Recovery of β -cell function, especially restoration of first-phase secretion of insulin, is likely to be one of the critical factors.^{1,2,9} Correction of glucotoxicity using intensive insulin therapy could reduce β -cell overload and provide a β -cell “rest” effect.⁹ Amelioration of glycemic markers, especially short-term markers such as 1,5AG, are indicators of elimination of glucotoxicity and, perhaps, β -cell rest. Furthermore, glycemic status also indirectly represents β -cell function or insulin resistance. Some recent studies showed that elevated FPG and 2hPG were associated with impaired β -cell function.^{10,11} Won et al.¹² also reported that 1,5AG correlated with the change in insulinogenic index by reflecting postprandial glucose. As for A1C, although it is widely used to monitor long-term glycemic control, its slow change after glycemic improvement limit its application in short-term intensive insulin therapy.

Although 1,5AG showed independent association with remission in this study, neither A1C nor FA independently predicted remission. This may due to different kinetics of these glycemic markers. FA and A1C represent average blood glucose over several weeks or months, respectively, by reflecting glycation of hemoglobin or serum proteins (FA) or hemoglobin (A1C). Therefore, changes of these glycemic markers correlate poorly with glucose fluctuation.^{13,14} In contrast, 1,5AG not only reflects changes of average glucose level, but also responds rapidly to glucose fluctuation.^{12,13,15,16} Yamanouchi et al.¹³ reported that 1,5AG was lower in patients with diabetes experiencing greater glucose fluctuation in spite of similar A1C levels; the decline of the 1,5AG level was reversible after glucose fluctuation was corrected. In a study performed in 55 patients with either type 1 diabetes or type 2 diabetes, 1,5AG was found to have a closer correlation than FA or A1C with mean postmeal maximum glucose and the area under the curve for glucose above 180 mg/dL in continuous glucose monitoring.¹⁴ It is well established that glucose fluctuation enhances oxidative stress, which can consequently induce β -cell damage and apoptosis.^{17–19} Moreover, 1,5AG preparation is found to attenuate the release of inflammatory

cytokines stimulated by lipopolysaccharides in *db/db* mice.²⁰ Reduction of islet inflammation may also play a role in β -cell function restoration.²¹

As mentioned above, there is still a lack of validated simple and accurate predictors of glycemic remission. Although recovery of AIR is considered to be a critical factor,^{1,2} it is not routinely practical because of inconvenient operation and high cost. Furthermore, as an indicator of first-phase insulin secretion induced by glucose, AIR represents only part of β -cell function. A study consisted of 48 newly diagnosed type 2 diabetes patients showed that the remission group had better improvement in HOMA-IR,²² which is also confirmed in this study. Given the critical role of eliminating glucotoxicity in recovery of β -cell function, it is reasonable to test a range of glycemic predictors for remission. Recently, in a study consisted of 84 newly diagnosed type 2 diabetes patients treated with CSII, decrease in both FPG and 2hPG after CSII predicted long-term remission.²³ However, in the stepwise logistic regression analysis in this study, 1,5AG at 1-month follow-up was the only glycemic marker that entered the final model. This indicated that 1,5AG at 1-month follow-up was the most sensitive among the evaluated glycemic predictors. Apparently, FPG or 2hPG alone may lose some glycemic information, for example, glycemic excursion. Moreover, as FPG and 2hPG are easily influenced by multiple medications or incidents, a single value of blood glucose is not reliable enough and needs to be confirmed, as we did in the study. 1,5AG, however, reflects both average and excursion of blood glucose in the short term. Additionally, 1,5AG is less likely to be influenced by temporal factors; thus, repeated confirmation of 1,5AG value is not necessarily required. These advantages of 1,5AG make it a reliable and easily implementable index of remission rather than other glycemic markers in this study. FPG or 2hPG can only act as an alternative choice if measuring 1,5AG is not approved or unavailable.

Although the increase in the 1,5AG level was predictive for remission 1 month after CSII was stopped, it did not show a predictive effect immediately after CSII. The reason lies in the kinetics of 1,5AG after improvement of glycemic control. Because most of the 1,5AG in the human body comes from diet, after amelioration of hyperglycemia, 1,5AG increases at a rate of about 0.3 mg/L per day and takes 5–10 weeks to reach a plateau.^{4,7,24} Therefore, the 1,5AG level at the end of CSII therapy was still in the ascending phase and was insufficient to distinguish remission from non-remission individuals. At 1-month follow-up, when optimum glycemic control had been achieved for about 6–7 weeks, the 1,5AG level had nearly reached its plateau and could fully reflect β -cell recovery and predict therapeutic response.

Although these findings are novel, there are still limitations. The major limitation of our study is the relatively small population size and short follow-up period. Because long-term glycemic outcome and β -cell function recovery are major concerns of early intensive insulin therapy, more data from prolonged follow-up and glycemic markers of different time points are required for future analysis and long-term validation.

In conclusion, our study shows that 1,5AG is a sensitive indication of glycemic changes and an independent predictor of remission in newly diagnosed patients with type 2 diabetes treated with short-term CSII. Further studies should validate this over the long term and also in clinical practice.

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Author Disclosure Statement

There are no conflicts of interest or competing financial information to report. The funding resources did not participate in any part of the study design, data collection, data analysis, data interpretation, or the report writing. The corresponding author had full access to all the data in study and had final responsibility for the decision to submit for publication.

References

- Li Y, Xu W, Liao Z, Yao B, Chen X, Huang Z, Hu G, Weng J: Induction of long-term glycemic control in newly diagnosed type 2 diabetic patients is associated with improvement of beta-cell function. *Diabetes Care* 2004;27:2597–2602.
- Weng J, Li Y, Xu W, Shi L, Zhang Q, Zhu D, Hu Y, Zhou Z, Yan X, Tian H, Ran X, Luo Z, Xian J, Yan L, Li F, Zeng L, Chen Y, Yang L, Yan S, Liu J, Li M, Fu Z, Cheng H: Effect of intensive insulin therapy on beta-cell function and glycemic control in patients with newly diagnosed type 2 diabetes: a multicentre randomised parallel-group trial. *Lancet* 2008;371:1753–1760.
- Ilkova H, Glaser B, Tunckale A, Bagriacik N, Cerasi E: Induction of long-term glycemic control in newly diagnosed type 2 diabetic patients by transient intensive insulin treatment. *Diabetes Care* 1997;20:1353–1356.
- Stickle D, Turk J: A kinetic mass balance model for 1,5-anhydroglucitol: applications to monitoring of glycemic control. *Am J Physiol* 1997;273:E821–E830.
- Yamanouchi T, Tachibana Y, Akanuma H, Minoda S, Shinohara T, Moromizato H, Miyashita H, Akaoka I: Origin and disposal of 1,5-anhydroglucitol, a major polyol in the human body. *Am J Physiol* 1992;263:E268–E273.
- Fluss R, Faraggi D, Reiser B: Estimation of the Youden Index and its associated cutoff point. *Biom J* 2005;47:458–472.
- McGill JB, Cole TG, Nowatzke W, Houghton S, Ammirati EB, Gautille T, Sarno MJ: Circulating 1,5-anhydroglucitol levels in adult patients with diabetes reflect longitudinal changes of glycemia: a U.S. trial of the GlycoMark assay. *Diabetes Care* 2004;27:1859–1865.
- Yamanouchi T, Ogata N, Tagaya T, Kawasaki T, Sekino N, Funato H, Akaoka L, Miyashita H: Clinical usefulness of serum 1,5-anhydroglucitol in monitoring glycemic control. *Lancet* 1996;347:1514–1518.
- Wajchenberg BL: Beta-cell failure in diabetes and preservation by clinical treatment. *Endocr Rev* 2007;28:187–218.
- Godsland IF, Jeffs JA, Johnston DG: Loss of beta cell function as fasting glucose increases in the non-diabetic range. *Diabetologia* 2004;47:1157–1166.
- Kohnert KD, Augstein P, Zander E, Heinke P, Peterson K, Freyse EJ, Hovorka R, Salzsieder E: Glycemic variability correlates strongly with postprandial beta-cell dysfunction in a segment of type 2 diabetic patients using oral hypoglycemic agents. *Diabetes Care* 2009;32:1058–1062.
- Won JC, Park CY, Park HS, Kim JH, Choi ES, Rhee EJ, Lee WY, Oh KW, Kim SW, Park SW: 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* 2009;84:51–57.
- Yamanouchi T, Moromizato H, Shinohara T, Minoda S, Miyashita H, Akaoka I: Estimation of plasma glucose fluctuation with a combination test of hemoglobin A1c and 1,5-anhydroglucitol. *Metabolism* 1992;41:862–867.
- Dungan KM, Buse JB, Largay J, Kelly MM, Button EA, Kato S, Wittlin S: 1,5-Anhydroglucitol and postprandial hyperglycemia as measured by continuous glucose monitoring system in moderately controlled patients with diabetes. *Diabetes Care* 2006;29:1214–1219.
- Yamanouchi T, Inoue T, Ogata E, Kashiwabara A, Ogata N, Sekino N, Yoshimura T, Ichiiyanagi K, Kawasaki T: Post-load glucose measurements in oral glucose tolerance tests correlate well with 1,5-anhydroglucitol, an indicator of overall glycemic state, in subjects with impaired glucose tolerance. *Clin Sci* 2001;101:227–233.
- Stettler C, Stahl M, Allemann S, Diem P, Schmidlin K, Zwahlen M, Riesen W, Keller U, Christ E: Association of 1,5-anhydroglucitol and 2-h postprandial blood glucose in type 2 diabetic patients. *Diabetes Care* 2008;31:1534–1535.
- Monnier L, Mas E, Ginot C, Michel F, Villon L, Cristol JP, Colette C: Activation of oxidative stress by acute glucose fluctuations compared with sustained chronic hyperglycemia in patients with type 2 diabetes. *JAMA* 2006;295:1681–1687.
- Donath MY, Ehses JA, Maedler K, Schumann DM, Ellingsgaard H, Eppler E, Reinecke M: Mechanisms of beta-cell death in type 2 diabetes. *Diabetes* 2005;54(Suppl 2):S108–S113.
- Robertson RP, Harmon J, Tran PO, Tanaka Y, Takahashi H: Glucose toxicity in beta-cells: type 2 diabetes, good radicals gone bad, and the glutathione connection. *Diabetes* 2003;52:581–587.
- Meng X, Tancharoen S, Kawahara KI, Nawa Y, Taniguchi S, Hashiguchi T, Maruyama I: 1,5-Anhydroglucitol attenuates cytokine release and protects mice with type 2 diabetes from inflammatory reactions. *Int J Immunopathol Pharmacol* 2010;23:105–119.
- Larsen CM, Faulenbach M, Vaag A, Volund A, Ehses JA, Seifert B, Mandrup-Poulsen T, Donath MY: Interleukin-1-receptor antagonist in type 2 diabetes mellitus. *N Engl J Med* 2007;356:1517–1526.
- Hu Y, Li L, Xu Y, Yu T, Tong G, Huang H, Bi Y, Weng J, Zhu D: Short-term intensive therapy in newly diagnosed type 2 diabetes partially restores both insulin sensitivity and beta-cell function in subjects with long-term remission. *Diabetes Care* 2011;34:1848–1853.

23. Xu W, Li YB, Deng WP, Hao YT, Weng JP: Remission of hyperglycemia following intensive insulin therapy in newly diagnosed type 2 diabetic patients: a long-term follow-up study. *Chin Med J (Engl)* 2009;122:2554–2559.
24. Yamanouchi T, Minoda S, Yabuuchi M, Akanuma Y, Akanuma H, Miyashita H, Akaoka I: Plasma 1,5-anhydro-D-glucitol as new clinical marker of glycemic control in NIDDM patients. *Diabetes* 1989;38:723–729.

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