

## Relationships of A1c Variability for 10 Years and Beta Cell Function at the Time of Diagnosis in Type 2 Diabetes

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### Abstract

**Background:** Recent several reports emphasized A1c variability along with average blood glucose determined by A1c. Many studies have been showing the relationship of A1c variability with chronic diabetic complications. But, associations between patterns or degrees of A1c variability and influential factors have not been studied much. Therefore, this study aimed to evaluate the relationships of A1c variability for 10 years and beta cell function at the time of diagnosis in type 2 diabetes in clinical practice.

**Methods:** Subjects of this study were 518 newly diagnosed type 2 diabetic patients. To evaluate beta cell function, we checked fasting c-peptide, glucose, and insulin and assessed homeostasis model assessment beta cell function index (HOMA- $\beta$ ) and homeostasis model assessment for insulin resistance (HOMA-IR) at the time of diagnosis. A1cs, fasting plasma glucose, and lipid profile were serially measured at least once in every year for 10 years.

**Results:** We found that higher A1c variability was associated with younger age at diagnosis of diabetes, lower BMI, higher first A1c, higher 2nd year A1c, and higher mean A1c. C-peptide and homeostasis model assessment beta cell function index were the highest in the low SD group and the lowest in high SD group.

**Conclusion:** A1c variability for 10 years in newly diagnosed type 2 diabetes is inversely related with the marker of beta cell function at the time of diagnosis.

**Keywords:** A1c Variability; Beta cell function; Type 2 diabetes

### Introduction

A1c is an important parameter of average blood glucose over several months in diabetic patients. It is well known that a level of glycemic control determined by A1c is an important marker for chronic complications of diabetes. Many studies have reported that lowering A1c reduces the risk and progression of diabetic complications [1,2].

In recent years, along with average blood glucose determined by A1c, glycemic variability has also been emphasized. The authors of DCCT study first suggested the role of glycemic variability in diabetic complications [3]. Since then, many in vivo and in vitro studies showed glucose fluctuation induced higher oxidative stress than sustained hyperglycemia, leading to dysfunction of vascular endothelium, renal mesangial and tubulointerstitial cell [4]. Our group also previously reported the effect of glucose fluctuation on pancreatic beta cell apoptosis and its mechanism [5,6]. These studies partially explained the relationship of glucose variability with chronic diabetic complications.

Recently, studies on A1c variability reflecting long-term glucose variability as well as acute glucose variability assessed with continuous glucose monitoring system (CGMS) have been published [7-9]. The long term variability (expressed as A1c variability) may be more important than short-term glucose variability as a risk marker for

diabetic complications because atherosclerosis is not a short-term event. Although there is a lack of evidence on the relationship between A1c variability and diabetic macrovascular complications, many studies have showed the relationship of glucose variability with chronic diabetic complications [7-11] and a recent retrospective cohort study reported that A1c variability can predict all-cause mortality in type 2 diabetic patients, independent of mean A1c and other confounders [9].

Glycemic variability in type 2 diabetes results from the complex interplay between pathophysiological factors, behavioural and treatment factors. Glycemic variability can be influenced by variable factors such as diet, exercise, medication and compliance during treatment. Unstable glucose fluctuations are more frequently shown in patients with type 1 diabetes than patients with type 2 diabetes and in patients with advanced type 2 diabetes in clinical practice. Therefore, the degrees of endogenous beta cell dysfunction in type 2 diabetes at the time of diagnosis may be one of important predictors for future glucose and A1c variability. There were few studies on the association of glucose variability with pancreatic beta cell dysfunction, but most of the studies had assessed the glucose variability with continuous glucose monitoring reflecting short-term glucose variability and evaluated the association with postprandial beta cell dysfunction [12]. In type 2 diabetes, the association between the degrees of glycemic variability and pancreatic beta cell dysfunction at the time of diagnosis has not been studied yet. Therefore, we investigated the A1c variability during the first 10 years after diagnosis of type 2 diabetes and evaluated the

relationship between glycemic variability and beta cell function at the time of diagnosis in type 2 diabetes.

## Methods

Inclusion criteria of our study were type 2 diabetes followed up in our institute for at least 10 years. All type 2 diabetic subjects were eligible to be recruited unless they were type 1 diabetic patients. Clinical data of 518 newly diagnosed diabetic patients including their baseline characteristics, including age, sex, height and weight were retrospectively collected. Body mass index (BMI) was calculated as follows: BMI=body weight in kg/(body height in meters)<sup>2</sup>. A1c levels, fasting plasma glucose, total cholesterol, triglycerides, low-density lipoprotein (LDL) cholesterol, and high-density lipoprotein (HDL) cholesterol were measured serially at least once in every year for 10 years since the patients were diagnosed as diabetes. At the time of diagnosis with type 2 diabetes, fasting c-peptide and insulin levels were assessed. For biochemical measurements, sampling was performed in the morning after an overnight fast (for ≥8 h). Serum fasting c-peptide and insulin were measured using a radioimmunoassay. The fasting glucose levels were measured with hexokinase method and hemolysed blood samples were excluded.

Intrapersonal SD of serially measured A1c was adjusted for a different number of assessments among patients using the equation of (adj-A1c-SD = SD/ $\sqrt{[n/(n - 1)]}$ ) and was used to express variability of A1c.

To evaluate beta cell function, we checked fasting c-peptide, glucose, and insulin and assessed homeostasis model assessment beta cell function index (HOMA-β) and homeostasis model assessment for insulin resistance (HOMA-IR) at the time of diagnosis.

Continuous variables are expressed as means ± SD if normally distributed. Categorical variables are expressed as percentages. Differences between patient groups were analyzed by Student t test (two groups) or ANOVA (over two groups) for normally distributed continuous variables. The chi-squared ( $\chi^2$ ) test was used for categorical variables. SPSS version 18.0 was used for statistical calculations. p <0.05 was considered statistically significant. Institutional Review Board was obtained by our institute.

## Results

### Clinical and biochemical characteristics

Of the 518 patients, 46.5% of patients were men and the mean age was 53.0 ± 12.2 years. To assess which patient characteristics were associated with A1c variability during the follow-up, we divided the patients into tertiles of intrapersonal SD of serially measured A1cs. Patients in the lowest, the middle and the highest tertile were referred as the low SD group, the middle SD group and the high SD group, respectively. The characteristics of these three groups were summarized in Table 1.

	SD of serial A1c		
	Low	Middle	High
No.	171	171	176
Age (years)	55.6 ± 11.5	52.9 ± 11.7 <sup>a</sup>	52.9 ± 12.9 <sup>a</sup>
BMI (kg/m <sup>2</sup> )	25.0 ± 2.89	24.2 ± 3.4	23.8 ± 3.2 <sup>a</sup>
Mean SD of A1c	0.54 ± 0.15	0.95 ± 1.12 <sup>a</sup>	1.79 ± 1.26 <sup>a,b</sup>
Mean First A1c (%)	6.47 ± 1.17	7.36 ± 1.45 <sup>a</sup>	9.01 ± 2.64 <sup>a,b</sup>
Mean 2nd year A1c (%)	6.21 ± 1.06	6.66 ± 1.28 <sup>a</sup>	7.02 ± 1.84 <sup>a,b</sup>
Mean (10yr) A1c (%)	6.48 ± 0.91	7.14 ± 0.78 <sup>a</sup>	7.78 ± 1.07 <sup>a,b</sup>
Total cholesterol (mg/L)	190.5 ± 30.9	198.0 ± 42.9	194.8 ± 55.8
LDL cholesterol (mg/L)	120.3 ± 29.2	125.8 ± 39.7	126.8 ± 47.4
HDL cholesterol (mg/L)	47.6 ± 13.5	48.2 ± 13.2	46.8 ± 15.1
Triglyceride (mg/L)	152.9 ± 105.8	165.2 ± 116.7	172.3 ± 124.7

**Table 1:** The characteristics of patients divided into tertiles of intrapersonal SD of serially measured A1cs for 10years. <sup>a</sup>p <0.05 vs low SD group, <sup>b</sup>p <0.05 vs middle SD group

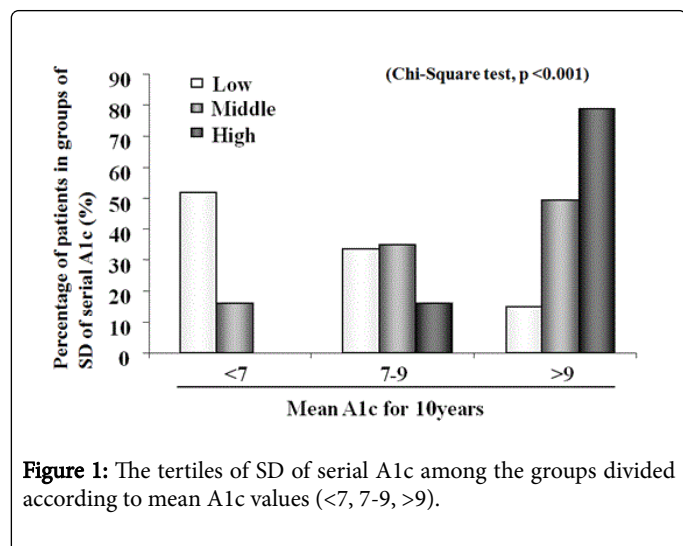
The patients in the high SD group were younger (55.6 ± 11.5 vs 52.9 ± 12.9 years) and had lower BMI than those in the low SD group (25.0 ± 2.89 vs 23.8 ± 3.2 kg/m<sup>2</sup>). The mean A1c levels of the low, middle and high SD group at the time of the diagnosis were 6.47 ± 1.17%, 7.36 ± 1.45 and 9.01 ± 2.64, respectively. The mean A1c levels of three groups at the second year were also significantly different (6.21 ± 1.06, 6.66 ± 1.28, 7.02 ± 1.84, p<0.05). The mean A1c level for 10years was the highest in the high A1c SD group and the lowest in the low A1c SD

group. Total cholesterol, LDL cholesterol, HDL cholesterol and triglyceride levels did not differ among the groups.

### Mean A1c and A1c variability

The patients were divided into 3 groups according to the range of the mean A1c value to evaluate the association between the mean A1c and A1c variability (Figure 1). In the patient group with the mean A1c for 10 years less than 7%, 51.7% of low SD of serial A1c were included.

In the group with the mean A1c over 9%, 78.9% of high SD group were included. There were significant differences among three groups ( $p < 0.001$ ).



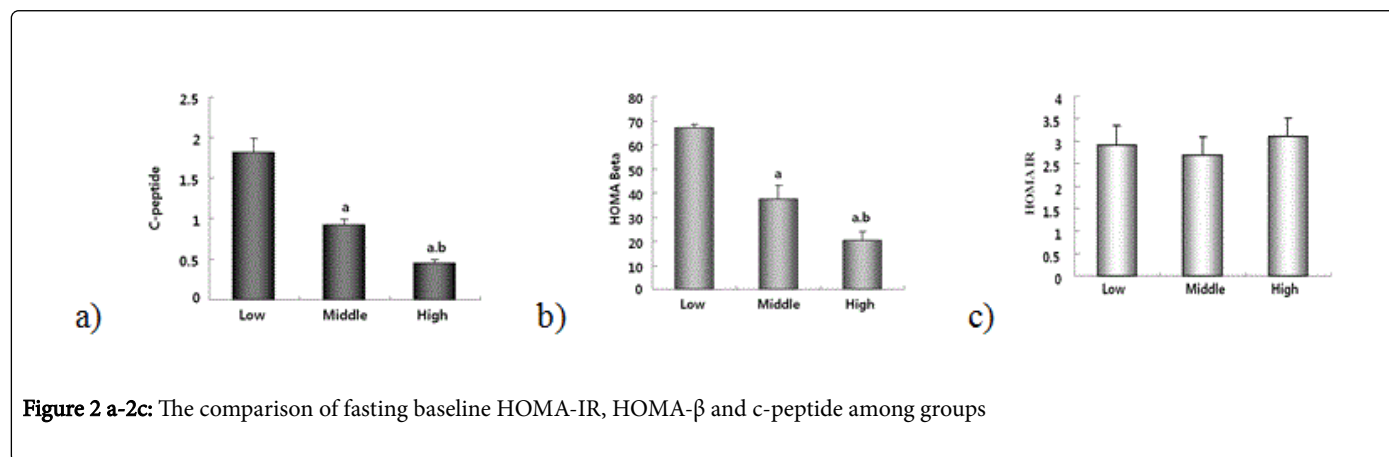
**Figure 1:** The tertiles of SD of serial A1c among the groups divided according to mean A1c values (<7, 7-9, >9).

### Relationships between A1c variability and beta cell function

We compared fasting baseline c-peptide, HOMA- $\beta$  and HOMA-IR among the SD groups to evaluate the relationship between A1c variability and beta cell function at the time of diagnosis. Fasting baseline c-peptide and HOMA- $\beta$  at the time of diagnosis were significantly different among the three groups ( $p < 0.05$ ), but HOMA IR did not significantly differ. C-peptide and HOMA- $\beta$  were the highest in the low SD group and the lowest in high SD group (Figure 2a-2c).

### Discussion

This study was conducted to investigate the relationship of A1c variability with beta cell function in type 2 diabetes in real clinical



**Figure 2 a-2c:** The comparison of fasting baseline HOMA-IR, HOMA- $\beta$  and c-peptide among groups

We tried to find the factors affecting the A1c variability which have been shown the association with diabetic complications and the higher A1c variability was associated with younger age at diagnosis of diabetes, lower BMI, higher first A1c, higher 2nd year A1c, and higher mean A1c in our result. Associations between patterns or degrees of A1c variability and influential factors have not been studied much. Several studies suggested that multiple factors including age, diabetic

practice. Recently, glycemic variability has also been emphasized and Monnier et al. have emphasized that glycemic variability is more important than chronic sustained hyperglycemia contributing to the development of secondary diabetes complications [13]. A1c variability relates to blood glucose changes over long periods of time. Increasing attention has been focused on A1c variability reflecting long-term glucose variability and diabetic complications and a number of studies have revealed the evidence on the relationship between A1c variability and diabetic complications in type 1 DM and type 2 DM. A retrospective analysis of the DCCT dataset had showed that variability in A1c adds to the mean value in predicting microvascular complications in type 1 diabetes. In that study, A1c variability is an independent risk factor for nephropathy and retinopathy independently of mean HbA1c in type 1 diabetic patients [7]. And, a report from the Finnish Nephropathy Study Group showed that A1c variability was not only predictive of incident microalbuminuria and progression of renal disease but also of incident CV disease events [8]. Also, HbA1c variability was shown to be an independent variable that increased the effect of HbA1c on the risk of microalbuminuria in adolescent patients with T1DM in the Oxford Regional Prospective Study and the Nephropathy Family Study [14]. There were several studies on the associations between the A1c variability and diabetic complications in type 2 DM. A1c variability affected the development of microalbuminuria independently of mean A1c in type 2 diabetes in the Tsukuba Kawai Diabetes Registry study [11]. A1c variability, even measured as early as 2 years, was independently associated with the development of microalbuminuria in a Taiwanese study [15]. Also, very recently in the Renal Insufficiency And Cardiovascular Events (RIACE) Italian Multicenter Study, A1c standard deviation was associated with macroalbuminuria and albuminuric stages 3-5 of chronic kidney disease, independently of average HbA1c, even after adjustment for other known predictors of diabetic nephropathy, whereas average HbA1c was not [16,17].

metabolic profiles, including BMI, waist circumference, systolic and diastolic blood pressure, total cholesterol, triglyceride, LDL-cholesterol and ALT, than those with higher A1c variability [9]. In our results, higher A1c variability was associated with younger age, lower BMI and higher mean A1c. The reason that younger patients have higher A1c variability may be because of younger patients' suboptimal management of diabetes (including of irregular life style). According to a study which analyzed changes in A1c during the first 6 years after diagnosis of type 2 diabetes, age was the only long-term predictor for changes in A1c [18]. A sharp rise in a long-term glycemic level was observed in a quarter of the patients, especially in the relatively young. In a previous study, it was found that lower BMI was associated with lower A1C variability and it was explained by mild insulin resistance. Nevertheless, lower BMI was associated with higher A1C variability in our study. This result can be explained by our other result that the patients with less endogenous beta cell function at the time of diagnosis showed the larger glucose variability.

And, we can find that A1c variability was inversely related with the marker of beta cell function at the time of diagnosis in our result. There were few studies on the association of glucose variability with pancreatic beta cell dysfunction. One study reported a nonlinear relationship between glycemic variability and beta cell dysfunction in type 2 diabetic patients [12]. In that study, short-term glucose variability assessed with continuous glucose monitoring system (CGMS) was associated with postprandial beta cell function. Another reported that glucose variability was significantly reduced in youth with short-term type 1 diabetes who retained residual  $\beta$ -cell function than in youth with type 1 diabetes for a longer duration [19]. However, we could not find the studies showing relationships between A1C variability and  $\beta$ -cell function at the time of diagnosis in type 2 diabetes. Our results supported that long-term glucose variability might have a correlation with endogenous beta cell defect at the time of diagnosis but not with insulin resistance. Based on the relationships between A1c variability and beta cell defect, we may also explain why young age and lower BMI are correlated with higher A1c variability.

There are some limitations in our study. This study was retrospectively conducted in a single clinic in Korea. And, there was no comprehensive analysis for hyperglycemic treatment modalities. We did not have information about the medications and the change of them for 10 years since our study is retrospective. We believe that physicians did their best to achieve optimal glycemic control in real practice. In other words, our results may represent real world status, not study setting.

In summary, A1c variability for 10 years in newly diagnosed type 2 diabetes is inversely related with the marker of beta cell function at the time of diagnosis. The A1c variability in type 2 diabetes may be reflected by dysfunction of the pancreatic beta cell at the time of diagnosis. We think that it is important to be aware of the association of these and applied to personalized treatment in type 2 diabetes.

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