# Comparison of Points in Range Measured by the Self-monitoring of Blood Glucose and Time in Range Measured by the Continuous Glucose Monitoring

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**Objective: Usage of time in range (TIR), measured by continuous glucose monitoring (CGM), has become common as a new index of glycemic control. Therefore, we compared points in range (PIR), measured by the self-monitoring of blood glucose (SMBG), with TIR.**
**Methods: In this prospective observational study, 43 patients with diabetes wore FreeStyle Libre Pro and conducted SMBG at the same time. Time above range (TAR), TIR, time below range (TBR) and points above range (PAR), PIR, points below range (PBR) were compared, respectively.**
**Results: The median PAR was 35.7%, while the median TAR was 20.8% for CGM. Conversely, the PIR was 64.3%, while the TIR was 74.9%; similarly, the PBR was 0%, while the TBR was 1.7%. A significant positive correlation was found between PIR and TIR ($r = 0.784$, $P < 0.001$). In the Bland-Altman analysis performed to assess the association between the two methods, PIR showed a −9.9% bias compared with TIR.**
**Conclusions: PIR may be used in patients who find it difficult to use CGM as a substitute of TIR, however caution is needed when interpreting the data due to the difference between PIR and TIR.**

**Key words: Time in range, points in range, continuous glucose monitoring, self-monitoring of blood glucose**

## INTRODUCTION

Glycated hemoglobin (HbA1c) has been the standard indicator of blood glucose control, however it has limitation of reduced accuracy in certain conditions, such as renal failure [1]. Furthermore, HbA1c does not reflect the degree of the glycemic variability. In some patients, HbA1c and mean blood glucose levels measured by SMBG or mean sensor glucose levels measured by CGM may present discrepancy. Therefore, current guidelines recommend assessing glycemic control using both CGM and measuring HbA1c levels. High HbA1c levels do not mean the patient is free from hypoglycemic episodes. Yoshii *et al*. reported that using CGM metrics to complement HbA1c monitoring may be beneficial, especially in older people, users of insulin and/or sulfonylureas, and patients with chronic kidney disease. PIR is considered to provide information beyond HbA1c, including fluctuations in blood glucose such as hypoglycemia and hyperglycemia [2]. On the other hand, the usage of time in range (TIR), measured by continuous glucose monitoring (CGM), has become common as a new index of glycemic control. In conjunction with TIR, the time below range (TBR) and the time above range (TAR) are used as the indicators of hypoglycemia and hyperglycemia [3]. There was negative correlation between HbA1c and TIR, and a TIR target of 70% corresponded to HbA1c less than 7% [4, 5].

One of the advantage of using HbA1c is that it is linked with the risk of microvascular complications such as retinopathy, nephropathy, and neuropathy, based on the observation in the Diabetes Control and Complications Trials (DCCT) [6]. Using the data of self-monitoring of blood glucose (SMBG) conducted during the DCCT, the percentage of the measurements within the range of 70−180 mg/dl was reported to have association with the development of diabetic retinopathy [7]. In another study which recruited 326 patients with type 2 diabetes, a close relationship was observed between the prevalence of retinopathy and the TIR measured by CGM [8].

On the other hand, skin problems and cost issues can be barriers to the use of CGM devices. Contact dermatitis was reported to be associated with deteriorated accuracy of CGM [9−11]. CGM and other advanced diabetes devices are not widely used among people with socio-economic deprivation or in developing countries [12, 13]. The points in range (PIR), defined as the percentage of measured values of SMBG within the target range (70−180 mg/dl), could be an alternative to TIR measured by CGM [14]. However, the studies which investigate PIR is limited so far. Therefore, we conducted a comparison of the PIR measured by SMBG and the

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TIR measured by CGM.

## MATERIALS AND METHODS

This is a single arm, prospective, observational study, that recruited 43 patients (8 with type 1 diabetes and 35 with type 2 diabetes) with type 1 or type 2 diabetes who wore the FreeStyle Libre Pro device (Abbott Diabetes Care, Alameda, CA, USA) as part of the routine diabetes care at the Tokai University Hospital. Inclusion criteria were; patients with type 1 or type 2 diabetes diagnosed according to the diagnostic criteria of the Japan Diabetes Society; aged 20 years or more; aged 85 years or less; who were self-injecting insulin, GLP-1 receptor agonists, or both; who performed SMBG at least 20 times a month; and who received an adequate explanation of the clinical study and provided free and voluntary written informed consent. Exclusion criteria were; pregnant women; planning to become pregnant the following year; being blind; had arteriovenous fistula in the right and left arms; using other implantable medical devices, such as pacemakers.

The FreeStyle Libre Pro was used for 10−14 days, and the data of SMBG measurements obtained for 2 days during the 10-day period, excluding the first and last three days of wearing the FreeStyle Libre Pro device, were used for the analysis. The frequency and timing of SMBG measurements were based on those reported in previous studies and were used to evaluate the usefulness of TIR [7]; the SMBG measurements were performed seven times a day before each meal, 90 minutes after each meal, and before bedtime. A blood glucose meter OneTouch Verio IQ (LifeScan, Malvern, PA, USA) was used for SMBG. No change of the treatment occurred during the study.

The mean blood glucose value, standard deviation (SD), TAR, TIR, and TBR were obtained from the CGM data, while the mean blood glucose value, SD, points above range (PAR), PIR, and points below range (PBR) were obtained from the SMBG data. The correlations among TIR, HbA1c, and glycated albumin (GA) levels, and between PIR and TIR were examined. Absolute changes in HbA1c resulting from PIR were also assessed across diabetes types, sexes, and age categories ($\geq 65$ vs. $< 65$ years) using analysis of covariance (ANCOVA). In addition, a Bland-Altman plot (difference plot) was used to evaluate the consistency between the two measurement methods. TIR and PIR were defined as the time or number of measurements within the target range (70−180 mg/dL); TAR and PAR as the higher value ranges; and TBR and PBR as the lower value ranges.

All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and/or with the Helsinki Declaration of 1964 and later versions. Informed consent or substitute for it was obtained from all patients for being included in the study. The study protocol was approved by the Clinical Study Review Board of the Tokai University School of Medicine (19R186), and written informed consent was obtained from all patients prior to the initiation of the study (UMIN000045896).

## RESULTS

Data obtained from 43 patients were used for the analysis. The patients' baseline characteristics are presented in Table 1. The median age was 63 years, and men accounted for 76.7% of the study population. 25 patients were treated only on insulin therapy, 8 patients were on GLP1 receptor analog injection with or without insulin, and 17 patients were taking oral blood glucose-lowering drugs (DPP4 inhibitors, metformin, SGLT-2 inhibitors, glinides) as adjunctive agents for injection drugs. Differences among modalities were not evaluated because of the small number of patients in each group.

With regard to the TAR, TIR, and TBR derived from the CGM data and the PAR, PIR, and PBR derived from the SMBG data, the median PAR was 35.7%, while the median TAR was 20.8% for CGM; the PIR was 64.3%, while the TIR was 74.9%; the PBR was 0%, while the TBR was 1.7% (Table 2). There was significant positive correlation between PIR and TIR ($r = 0.784$, $P < 0.001$) (Table 3). The PIR and TIR were negatively correlated with pre-prandial, 90-minute post-prandial, and before-bedtime SMBG measurements (Table 4). The correlation coefficients showed the strongest correlation between TIR and the measurements obtained before lunch ($r = -0.754$), while the weakest correlation was observed between TIR and the measurements obtained before dinner ($r = -0.452$). There were no significant differences in adjusted HbA1c changes across diabetes types ($P = 0.315$ [ANCOVA]), sexes ($P = 0.441$ [ANCOVA]), or age categories ($P = 0.908$ [ANCOVA]).

In the Bland-Altman analysis , PIR showed a −9.9% bias compared with TIR (Fig. 1). With regard to the relationship between PIR, TIR and HbA1c, a 10% increase in PIR and TIR was associated with a 0.46% and a 0.36% decrease in HbA1c levels, respectively.

## DISCUSSION

There was significant positive correlation between PIR calculated from SMBG data and TIR calculated from CGM data. Both the PIR and TIR were significantly correlated with HbA1c or GA levels. The correlation was strongest for measurements obtained before lunch and weakest before dinner. There was −9.9% negative bias in PIR compared to TIR.

A previous studies conducted in patients with type 1 diabetes using CSII reported a significantly lower median PIR derived from the SMBG compared to TIR derived from the rtCGM data [15]. The lower PIR might be attributed to the inability to obtain the SMBG data during night-time sleep; furthermore, four of the seven measurements were taken after meal, reflecting a high blood glucose level and thus considered an influencing factor. These findings should serve as a guide when using PIR in the clinical setting. They also suggest the need for further elaboration of the timing of SMBG measurements, which will be discussed later.

This study examined the correlation between TIR and the timing of SMBG measurements; there is possibility that breakfast and lunch are scheduled at the same time each day to some extent, whereas dinner time and the amount of activity performed before dinner varied widely from day to day. In addition,

**Table 1** Characteristics of the participants

| Variables | Median (25%, 75%) |
|---|---|
| Diabetes type (Type 1, Type 2), % | 18.6, 81.4 |
| Sex (Male, Female), % | 76.7, 23.3 |
| Age, years | 63 (51.5, 70.5) |
| Age category ( ≥ 65 years, < 65 years), % | 48.8, 51.2 |
| BMI, kg/m$^2$ | 24.1 (22.8, 26.2) |
| SBP, mmHg | 129 (121.5, 135.5) |
| DBP, mmHg | 79 (69.5, 83.5) |
| HbA1c, % | 7.5 (6.8, 8.2) |
| GA, % | 19.2 (16.7, 21.2) |
| Alb, g/dL | 4.1 (3.9, 4.4) |
| Hb, g/dL | 13.9 (12.6, 15.1) |
| Ht, % | 41.7 (38.3, 44.5) |
| eGFR, mL/min/1.73m$^2$ | 63.0 (47.0, 72.0) |
| uAlb, mg/g・Cr | 30 (16, 93) |

Numbers are percentage or median [25%, 75%]. BMI, body mass index; SBP, systolic blood pressure; DBP, diastolic blood pressure; HbA1c, glycated hemoglobin; GA, glycated albumin; Alb, albumin; Hb, hemoglobin; Ht, hematocrit; eGFR, estimated glomerular filtration rate; uAlb, urinary albumin.

**Table 2** Comparison of TIR and PIR

| Variables | Median (25%, 75%) |
|---|---|
| CGM-based | |
| Mean glucose, mg/dL | 141.0 (120.9, 157.1) |
| SD | 45.1 (37.2, 52.6) |
| TAR | 20.8 (10.1, 29.5) |
| TIR | 74.9 (66.7, 86.3) |
| TBR | 1.7 (0.0, 5.1) |
| SMBG-based | |
| Mean glucose, mg/dL | 173.8 (152.5, 188.0) |
| SD | 47.6 (34.1, 67.3) |
| PAR | 35.7 (21.4, 50.0) |
| PIR | 64.3 (50.0, 78.6) |
| PBR | 0.0 (0.0, 0.0) |

N = 43. Median (25%, 75%). Numbers are percentage or median [25%, 75%]. CGM, continuous glucose monitoring; SD, standard deviation; TAR, time above range; TIR, time in range; TBR, time below range; SMBG, self-monitoring of blood glucose; PAR, points above range; PIR, points in range; PBR, points below range.

**Table 3** Correlation between HbA1c or GA and TIR or PIR

| Variables | PIR | | TIR | |
|---|---|---|---|---|
| | r | *P* value | r | *P* value |
| HbA1c | -0.646 | < 0.001* | -0.762 | < 0.001* |
| GA | -0.537 | < 0.001* | -0.624 | < 0.001* |

* $P < 0.05$. HbA1c, glycated hemoglobin; GA, glycated albumin; PIR, points in range; TIR, time in range.

**Table 4** Correlation between SMBG and TIR or PIR

| Variables | PIR | | TIR | |
|---|---|---|---|---|
| | r | *P* value | r | *P* value |
| SMBG Mean | -0.829 | < 0.001* | -0.732 | < 0.001* |
| Timing, 1 time | | | | |
| Breakfast, pre | -0.575 | < 0.001* | -0.564 | < 0.001* |
| Breakfast, post | -0.715 | < 0.001* | -0.658 | < 0.001* |
| Lunch, pre | -0.710 | < 0.001* | -0.754 | < 0.001* |
| Lunch, post | -0.593 | < 0.001* | -0.548 | < 0.001* |
| Dinner, re | -0.438 | 0.003* | -0.452 | 0.003* |
| Dinner, post | -0.734 | < 0.001* | -0.500 | < 0.001* |
| Bedtime | -0.757 | < 0.001* | -0.597 | < 0.001* |
| Preprandial, 3 times | -0.641 | < 0.001* | -0.586 | < 0.001* |
| Postprandial, 3 times | -0.748 | < 0.001* | -0.752 | < 0.001* |

* $P < 0.05$. SMBG, self-monitoring of blood glucose; PIR, points in range; TIR, time in range.

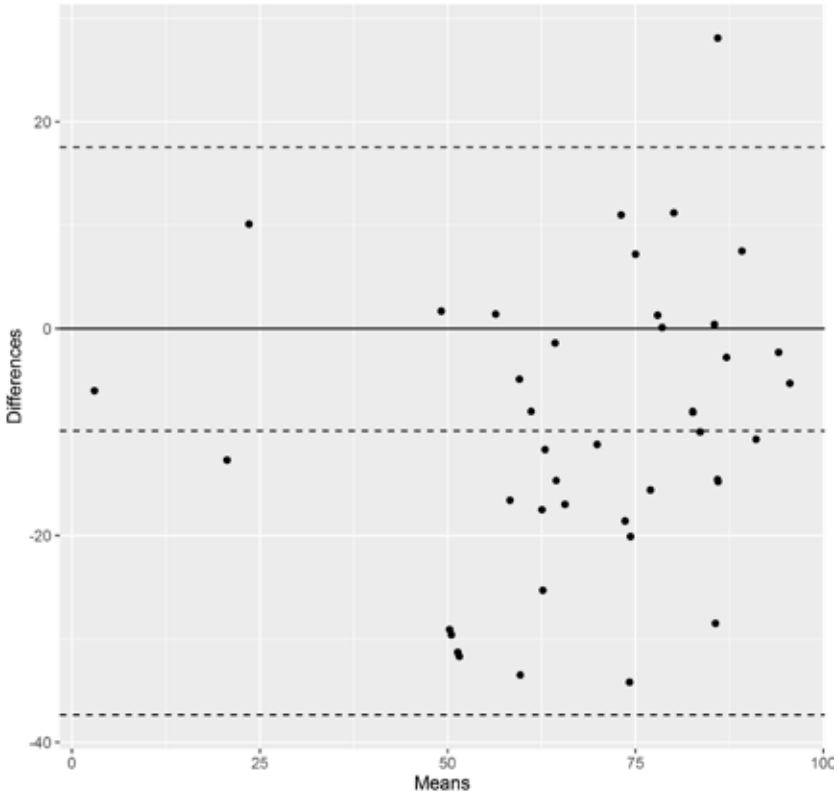


**Fig. 1** Bland-Altman analysis comparing the PIR and the TIR.
The horizontal axis represents the means of the two methods and the vertical axis represents the difference of the two methods. There was bias of −9.9 % when the PIR levels were compared to the TIR levels, with ULoA being 17.5 % and LLoA −37.3 %.

the correlation between TIR and SMBG was stronger post-prandially than that measured thrice pre-prandially; this finding suggests that adding postprandial measurements to the self-management program from time to time to indirectly estimate the TIR, rather than just continuously measuring the SMBG three times before each meal, would lead to an improvement in self-care practice.

In addition, to effectively use PIR in the actual clinical practice, the time zone in which SMBG measurement is most correlated with TIR, or the time zone that is correlated with TBR needs to be determined not only based on measurements obtained seven times a day, as reported in this study, but also in various time zones.

Caution should be exercised when interpreting the data of this study and applying PIR in the actual clinical practice. Patients tend to modify their diet and level of exercise during the 2-day SMBG in order to calculate the PIR. Therefore, the blood glucose levels may be lower, and the PIR may be overestimated. Therefore, patients should be instructed to calculate the PIR based on the measurements taken during their normal daily routine. In this study, the patients were asked to calculate the PIR on any 2 days during the 10-day period; however, the measurements taken for 3 days (e.g., two weekdays plus one holiday) would more accurately reflect the TIR. Hence, further studies are required to determine the appropriate number of days to perform these measurements.

With regard to the compatibility between PIR and TIR based on the results of this study, if the term "compatible" was defined as a relative error within 20% and a measurement frequency of at least 75% was used, the result was 54.8%, thus indicating that incompatibility.

In terms of the clinical application of PIR, the results of this study showed no significant correlation between diabetes type, age, or sex as factors affecting PIR, suggesting that PIR can be applied to a relatively wide range of patients. In fact, recent clinical studies have reported results using PIR derived from SMBG instead of HbA1c as an evaluation index [16, 17], and its clinical application may be expected as one of the new evaluation indices for glycemic control in the near future.

In conclusion, the PIR may be used in patients who find it difficult to TIR, however caution is needed when interpreting the data due to the difference between PIR and TIR.

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An abstract of this study in Japanese was presented at the 65h annual meeting of the Japan Diabetes Society in Kobe, Japan, 12–14 May 2022.

## CONFLICT OF INTEREST

Masao Toyoda received lecture fee from Abbott, Boehringer Ingelheim, Eli Lilly, Novo Nordisk, Sumitomo, Mitsubishi Tanabe and received research grant from Cocokara Fine Healthcare, LifeScan, Roche DC and Super Light Water. Takashi Murata received research grant from Medtronic. Other author declares no conflict of interest.

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