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ORIGINAL ARTICLE

Evaluation of a Minimally Invasive System for Measuring Glucose Area under the Curve during Oral Glucose Tolerance Tests: Usefulness of Sweat Monitoring for Precise Measurement

Kazuhiko Sakaguchi, M.D., Ph.D.,[1] Yushi Hirota, M.D., Ph.D.,[1] Naoko Hashimoto, M.D., Ph.D.,[1] Wataru Ogawa, M.D., Ph.D.,[1] Tomoya Hamaguchi, M.D., Ph.D.,[2] Toshihiro Matsuo, M.D., Ph.D.,[3] Jun-ichiro Miyagawa, M.D., Ph.D.,[3] Mitsuyoshi Namba, M.D., Ph.D.,[2,3] Toshiyuki Sato, M.Sc.,[4] Seiki Okada, M.Sc.,[4] Koji Tomita, M.D., Ph.D.,[5] Munehide Matsuhisa, M.D., Ph.D.,[6] Hideaki Kaneto, M.D., Ph.D.,[7] Keisuke Kosugi, M.D., Ph.D.,[8] Hiroshi Maegawa, M.D., Ph.D.,[9] Hiromu Nakajima, M.D., Ph.D.,[5] and Atsunori Kashiwagi, M.D., Ph.D.[9]

Abstract

Aims:

We developed a system for measuring glucose area under the curve (AUC) using minimally invasive interstitial fluid extraction technology (MIET). Sweat contamination during interstitial fluid glucose (IG) extraction affects the accuracy of glucose AUC measurement, because this technology uses extracted sodium ion levels as an internal standard. Therefore, we developed a sweat monitoring patch to reduce this effect and investigated its efficacy in volunteers undergoing oral glucose tolerance tests (OGTTs).

Materials and Methods:

Fifty diabetes mellitus inpatients and 10 healthy subjects undergoing the 75 g OGTT were included. Two sites on the forearm were pretreated with microneedle arrays, then hydrogels for interstitial fluid extraction were placed on the treated sites. Simultaneously, hydrogels for sweat monitoring were placed on untreated sites near the treated sites. Plasma glucose (PG) levels were measured every 30 min for 2 h to calculate reference AUC values. Using MIET, IG AUC was calculated from extracted glucose and sodium ion levels after attachment of the hydrogel for 2 h.

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Author Affiliations: [1]Division of Diabetes and Endocrinology, Kobe University Graduate School of Medicine, Kobe, Japan; [2]Division of Innovative Diabetes Treatment, Department of Internal Medicine, Hyogo College of Medicine, Hyogo, Japan; [3]Division of Diabetes and Metabolism, Department of Internal Medicine, Hyogo College of Medicine, Hyogo, Japan; [4]Central Research Laboratories, Sysmex Corporation, Kobe, Japan; [5]Department of Clinical Laboratory, Osaka Medical Center for Cancer and Cardiovascular Diseases, Osaka, Japan; [6]Diabetes Therapeutics and Research Center, The University of Tokushima, Tokushima, Japan; [7]Department of Metabolic Medicine, Osaka University Graduate School of Medicine, Osaka, Japan; [8]Department of Internal Medicine, Osaka Police Hospital, Osaka, Japan; and [9]Department of Medicine, Shiga University of Medical Science, Shiga, Japan

Abbreviations: (ADA) American Diabetes Association, (AUC) area under the curve, (CGM) continuous glucose monitoring, (DM) diabetes mellitus, (FPG) fasting plasma glucose, (IDF) International Diabetes Federation, (IG) interstitial fluid glucose, (IRI) immunoreactive insulin, (ISF) interstitial fluid, (MIET) minimally invasive interstitial fluid extraction technology, (OGTT) oral glucose tolerance test, (PG) plasma glucose, (SMBG) self-monitoring of blood glucose

Keywords: glucose area under the curve, glucose monitoring, glycemic excursion, interstitial fluid glucose, sweat monitoring

Corresponding Author: Kazuhiko Sakaguchi, M.D., Ph.D., Division of Diabetes, Metabolism, and Endocrinology, Kobe University Graduate School of Medicine, 7-5-1 Kusunoki-cho, Chuo-ku, Kobe 650-0017, Japan; email address kzhkskgc@med.kobe-u.ac.jp

Abstract cont.

Results:

Good correlation between IG AUC measurements using MIET and reference AUCs measured using PG levels was confirmed over a wide AUC range (202–610 mg/h/dl) after correction for the sweat-induced error detected by the hydrogel patches on the nonpretreated skin. Strong correlation between IG AUC and peak glucose levels indicates that glucose spikes can be easily detected by this system.

Conclusion:

We confirmed the effectiveness of a sweat monitoring patch for precise AUC measurement using MIET. This novel, easy-to-use system has potential for glucose excursion evaluation in daily clinical practice.

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Introduction

The incidence of type 2 diabetes mellitus (DM) is rapidly increasing.[1] This condition often leads to decreased quality of life, increased medical costs, and early death because of DM-associated complications. The Diabetes Epidemiology Collaborative Analysis of Diagnostic Criteria in Europe and Diabetes Epidemiology Collaborative Analysis of Diagnostic Criteria in Asia studies have shown that the presence of hyperglycemia after a glucose load is associated with elevated risk for cardiovascular disease, even in individuals with pre-DM.[2,3] Therefore, diabetologists have focused on the long-term control of microvascular/macrovascular complications by managing postprandial hyperglycemia from the early stages of DM. Some studies have suggested that α-glucosidase inhibitors are effective for preventing cardiovascular diseases by suppressing postprandial hyperglycemia.[4,5]

Guidelines published by the American Diabetes Association (ADA) and the International Diabetes Federation (IDF) stress the importance of postprandial hyperglycemia management.[6,7] For example, the IDF guidelines recommend that 2 h postprandial plasma glucose (PG) levels should not exceed 160 mg/dl, provided hypoglycemia does not occur.[7] However, there is no consensus on a universally accepted evidence-based definition of postprandial hyperglycemia, compared with the established importance of 2 h PG levels during oral glucose tolerance tests (OGTTs).[8–10]

The guidelines also recommend self-monitoring of blood glucose (SMBG), if possible. However, accurate estimation of postprandial hyperglycemia using SMBG is difficult because glucose levels vary greatly over time. Furthermore, frequent measurements cause pain and inconvenience to the patient. Continuous glucose monitoring (CGM) provides useful information to DM patients who require precise glycemic control.[11] However, CGM is cumbersome for non-insulin treated type 2 DM patients because of the requirement to insert needles and use blood samples for calibration, which is in addition to the cost. Some new methodologies can reportedly ameliorate these problems, but none are currently available on the market.[12,13]

Here we report a novel method using minimally invasive interstitial fluid extraction technology (MIET) to measure postprandial glucose excursion estimated using a glucose area under the curve (AUC) value.[14] This value corresponds to the total glucose increase after glucose loading, and consideration of the timing of blood sampling is unnecessary with this technique. The glucose AUC value after glucose loading can be monitored by placing a hydrogel patch on a pretreated skin area for a predefined period to accumulate interstitial fluid glucose (IG), as shown in **Figure 1**. This system enables convenient monitoring of glucose AUC, which acts as a surrogate of postprandial hyperglycemia, without blood sampling.

Sato and coauthors[14] conducted a feasibility study of MIET on healthy subjects and showed a strong correlation between IG AUC and glucose AUC as determined by postprandial SMBG. The accuracy of the measurement system was next evaluated by measuring IG AUC during OGTTs administered to individuals with and without DM in order to compare IG AUC with reference PG AUC values.[15] However, the effects of sweating were not considered in these studies. In principle, sodium ion and glucose levels in sweat are likely to interfere with IG AUC measurement using MIET, because both sodium ion and glucose levels are extremely low in interstitial fluid (ISF) and may compromise the accuracy of measurement. Therefore, we developed a sweat monitoring patch for use during IG accumulation.

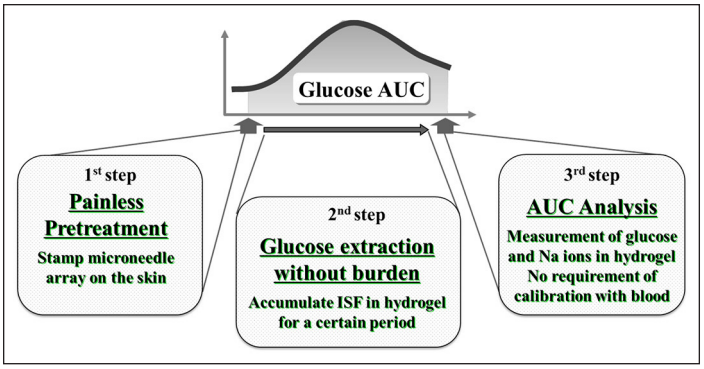

Figure 1. Measurement sequence used in the minimally invasive glucose AUC monitoring system. Glucose AUC for a predefined period can be measured by placing a hydrogel patch for the desired period without blood sampling for calibration.

In the present study, we determined the usefulness of sweat monitoring for precise IG AUC measurement using MIET by evaluating the accuracy of measurement after the application of sweat monitoring patches to patients with DM and healthy subjects undergoing OGTTs.

Material and Methods

Clinical Evaluation Protocol

Using MIET, IG AUC measurement was performed during OGTT administration to 50 inpatients with DM and 10 healthy volunteers using ISF collected from the forearm skin. The collection sites were wiped with an antiseptic; hairless sites were selected in order to avoid the pain caused by removal of the adhesive tape of the hydrogel patch and to maintain contact between the hydrogel patch and skin surface. Next, microneedle arrays were stamped onto two sites using a microneedle applicator. Each hydrogel patch contained a hydrogel for ISF accumulation at the pretreated site and another for sweat detection at the untreated site. Two hydrogel patches were placed on pretreated sites to collect ISF and monitor sweat production. Following consumption of a 75 g oral glucose load, PG and immunoreactive insulin (IRI) levels were measured every 30 min for 2 h. After the final PG measurement, the hydrogel patches were removed and analyzed for the quantities of ISF and sweat. All participants were requested to fill out questionnaires concerning their impression of the hydrogel patch, erythema, and pain associated with the stamping process.

Plasma glucose, IRI, glycated hemoglobin (converted to the values of the National Glycohemoglobin Standardization Program standards),[16] and serum sodium levels were measured using a conventional, routinely calibrated, clinical laboratory system.

The nature of this study was explained to the participants and detailed informed consent was obtained from each subject. The study was conducted under strict adherence to the latest version of the Declaration of Helsinki; all protocols were approved by the ethics committee of Kobe University (Kobe, Japan) and Hyogo College of Medicine (Hyogo, Japan).

Apparatus and Materials

The microneedle array was composed of polycarbonate plastic containing 305 needles, each 0.3 mm in length. It covered a circular area of approximately 50 mm^2. The applicator for microneedle stamping of the skin was a spring action, handheld system.

The hydrogel patch comprised two hydrogels and adhesive tape (KP; Nichiban, Tokyo, Japan). The hydrogels were made of polyvinyl alcohol containing 2% potassium chloride. The hydrogel for ISF accumulation was circular, and that

for sweat detection was rectangular, because this enables the user to discriminate accurately between hydrogels by shape before analysis of their contents (**Figure 2**). These hydrogels were placed close to each other on the forearm to reduce the effect of the sweat profile, which minimized the effect of sweat variation among individuals. The area of each hydrogel was approximately 80 mm^2. The reagent for glucose analysis was described previously.[15]

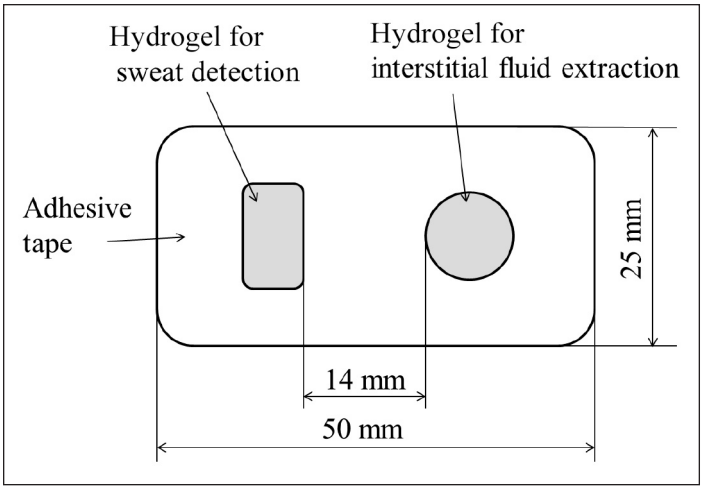

Figure 2. Diagram of a hydrogel patch.

Procedures for Glucose/Sodium Ion Analyses

The hydrogels were separated from the adhesive tape prior to analysis and incubated in 1.6 ml of pure water at 50 °C for >3 h to extract glucose and sodium ions. For glucose measurement, 0.1 ml of the sample solution was mixed with 0.1 ml of the fluorochrome reagent. After a 60 min incubation period, the intensity of the fluorochrome was measured using a fluorescence plate reader (MTP-800AFC; Corona Electric Co. Ltd., Ibaragi, Japan). Sodium ion levels were analyzed using a sodium ion-selective electrode (C-122; Horiba Cardy, Kyoto, Japan) and a potassium ion-selective electrode (C-131; Horiba Cardy) for correction of potassium ion interference.

Data Analysis Methods

Reference PG AUCs were calculated by trapezoidal approximation of PG levels measured every 30 min.

IG AUC was calculated on the basis of the measured level of glucose [M_{glu} (nmol)] and sodium ions [M_{Na} (nmol)] in the hydrogel for ISF accumulation and sodium ion level [M_{Na}* (nmol)] in the hydrogel for sweat detection as follows:

$$\text{IG AUC (mg/h/dl)} = \frac{M_{glu}}{a(M_{Na} - b \times M_{Na}^*) \ / \ (C_{Na} \times T)}$$

where T is the measured accumulation time for IG, C_{Na} (mM) is a constant indicating the sodium ion level in the skin, a (0.25) is the calibration coefficient of permeability between glucose and sodium ions and unit conversion, and b (0.9345) is the calibration constant of the difference between the sizes of the hydrogel patches used for ISF extraction (A(cm^2)) and sweat detection (A^*(cm^2)). $M_{Na} - b \times M_{Na}^*)/T$ indicates the extraction rate of sodium ion from ISF, which is a surrogate of the pore size produced by microneedle application. Through dividing M_{glu} (total glycemic excursion) by the pore size, the standardized total glycemic excursion (IG AUC) can be calculated. The principles and details of data analysis have been described previously.[14]

Indices for the detection of sweat error were calculated as follows:

$$\text{Sweat Ratio} = \frac{b \times M_{Na}^*}{M_{Na} - b \times M_{Na}^*}$$

$$\text{Sweat Rate (μm/h)} = bM_{Na}^* \ / \ (T \times A^* \times C_{Na}) \times 10$$

$$\text{ISF Extraction Rate (μm/h)} = (M_{Na} - b \times M_{Na}^*) \ / \ (T \times A \times C_{Na}) \times 10$$

Sweat rate and ISF extraction rate are dimensions of sodium ion permeability through the skin for sweat and ISF, respectively.

Results

Baseline Patient Information and Oral Glucose Tolerance Test Results

Baseline information, OGTT results, and participant characteristics are shown in **Table 1**. The healthy subjects were younger and had lower body mass indices compared with the DM inpatients. Despite the fasting plasma glucose (FPG) levels being similar between the DM inpatients and healthy subjects, glycemic excursions after glucose loading were significantly different between the DM inpatients and the healthy subjects. This subsequently led to a large difference in PG AUC levels. In contrast, IRI AUC levels were nearly equal among the healthy subjects and DM inpatients. However, the peak time of IRI was later in the DM inpatients than in the healthy subjects.

The range of serum sodium ion levels was limited in the DM inpatients, suggesting that the estimation of ISF extraction rates using sodium ion levels was appropriate.

Table 1.
Patient Characteristics and Oral Glucose Tolerance Test Results for the Inpatients with Diabetes Mellitus and Healthy Subjects[a]

		DM subjects	Healthy subjects
N		50	10
Age		55.2 ± 14.5	25.6 ± 2.6
Sex (M/F)		24/26	6/4
BMI		24.5 ± 5.4	20.8 ± 1.1
HbA1c (%)		7.1 ± 2.3	N.A.
Serum sodium (mM)		141 ± 1.7	N.A.
PG (mg/dl)	0	95 ± 17	92 ± 5
	30	162 ± 38	139 ± 28
	60	197 ± 58	128 ± 30
	90	205 ± 82	135 ± 20
	120	204 ± 102	114 ± 12
PG AUC (mg/h/dl)		356 ± 106	247 ± 35
IRI (mU/liter)	0	6.6 ± 5.2	5.3 ± 1.9
	30	33 ± 29	70 ± 58
	60	44 ± 39	47 ± 31
	90	57 ± 62	49 ± 24
	120	51 ± 61	34 ± 18
IRI AUC (mU/h/liter)		81 ± 72	89 ± 43

[a] Data are presented as mean ± standard deviation. BMI, body mass index; HbA1c, glycated hemoglobin; N.A., not available.

Detection of Sweat-Induced Measurement Error

Figure 3 shows the correlation between the IG AUC/PG AUC ratio, which indicates the accuracy of IG AUC measurement, and the indices for the detection of sweat-induced measurement error. The IG AUC/PG AUC ratio was clearly dependent on the (A) sweat ratio, (B) sweat rate, and (C) ISF extraction rate. As described in Materials and Methods, the sweat ratio is the quotient of sweat rate divided by ISF extraction rate; therefore, a larger sweat ratio indicates a less accurate IG AUC measurement (**Figure 3A**), as does a higher sweat rate (**Figure 3B**). In contrast, a high ISF extraction rate can decrease the contribution of sweat to measurement error as shown in **Figure 3C**. To eliminate sweat error completely and effectively, threshold levels of

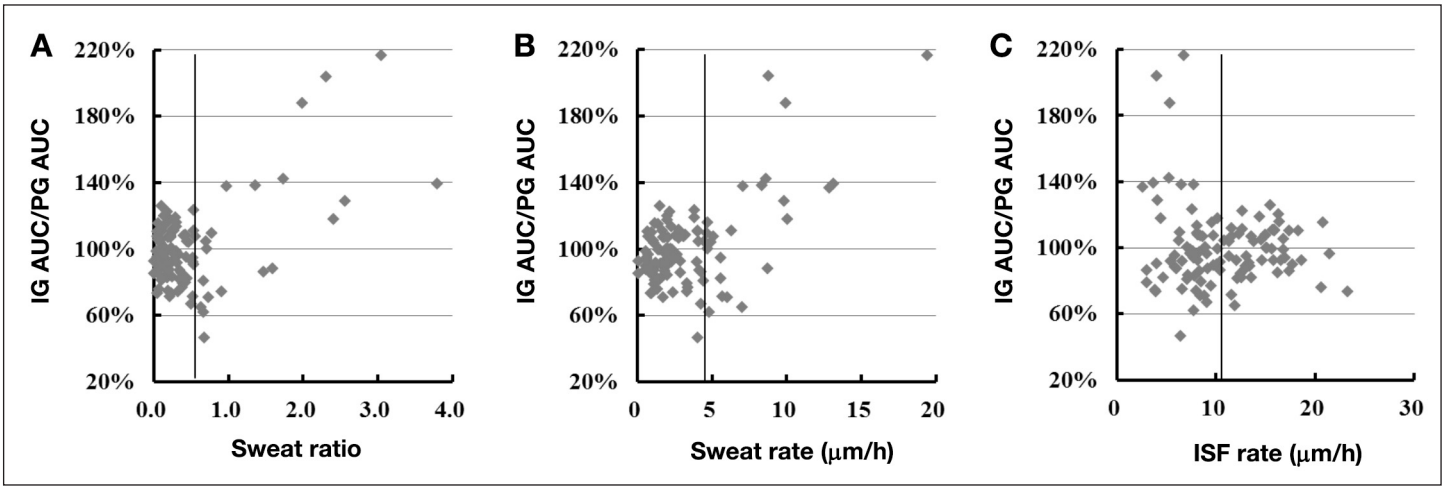

Figure 3. The dependency of IG AUC/PG AUC ratio on **(A)** sweat ratio, **(B)** sweat rate, and **(C)** ISF extraction rate.

0.62, 4.8, and 10.8 μm/h were used for sweat ratio, sweat rate, and ISF rate, respectively. The rate of exclusion of data points using these thresholds was 18% for all measurements, except the experimental error caused by hydrogel patch handling, use of cosmetics at the sampling site, or other reasons not dependent on sweat.

Accuracy of Interstitial Fluid Glucose Area under the Curve Measurement

Figure 4 shows the correlation between PG AUC and IG AUC after the elimination of sweat-induced measurement error, as defined by the previously mentioned criteria. The correlation coefficient was sufficiently high (R = 0.90) over a wide range of AUCs (202–610 mg/h/dl). A Bland–Altman plot showed that the majority of data were within 20% of the reference PG AUC level (**Figure 4B**). The degree of error was not clearly dependent on the reference AUC level. The reproducibility of two simultaneous IG AUC measurements was 6.2% (coefficient of variance), and the mean absolute percentage error was 11.4%.

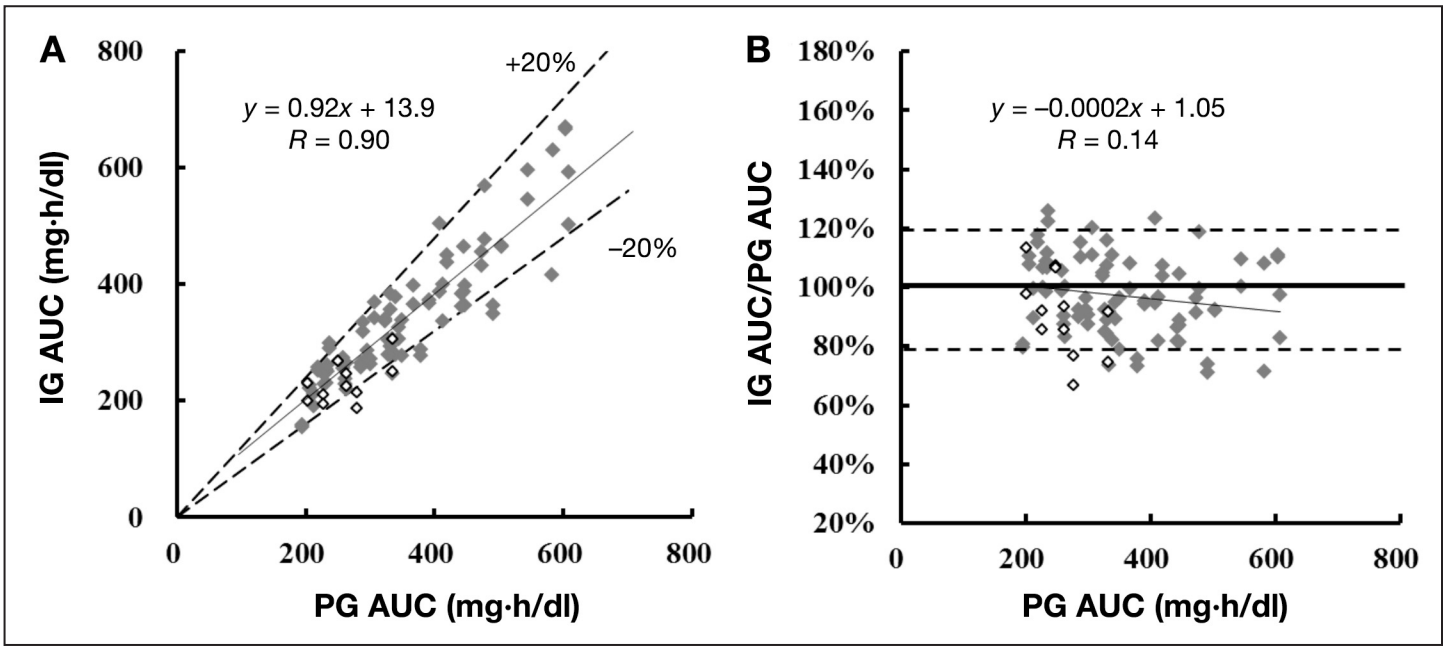

Figure 4. The accuracy of IG AUC measurement after elimination of sweat-induced measurement error: **(A)** the correlation between PG AUC and IG AUC and **(B)** a Bland–Altman plot of IG AUC/PG AUC versus PG AUC. Closed and open squares indicate inpatients with DM and healthy subjects, respectively.

Correlation between Interstitial Fluid Glucose Area under the Curve and Plasma Glucose Levels

In accordance with a previous study,[15] good correlation was confirmed between peak PG levels and IG AUC or PG AUC (R = 0.87 for IG AUC and R = 0.96 for PG AUC in **Figures 5A** and **5B**), suggesting that peak glucose levels can be detected simply and precisely by MIET without blood sampling. The strong correlation between IG AUC and PG levels at 1 h (R = 0.86) indicated that the time of peak PG level occurred mostly at 1 h after glucose loading (**Figure 5C**), explaining the weaker correlation between IG AUC and PG levels at 2 h (R = 0.82; **Figure 5D**). The weak correlation between IG AUC and FPG levels marks the limitation of using FPG alone to predict glycemic excursion after glucose loading (**Figure 5E**).

Adverse Effects

No bleeding was observed after skin stamping using the microneedle array or during or after ISF collection. **Table 2** lists the results of the questionnaire concerning pain caused by the stamping process and venous blood sampling, the impression left by the hydrogel patch, and scarring at the stamped area. As shown, the majority of patients reported neither pain nor discomfort from the skin stamping process.

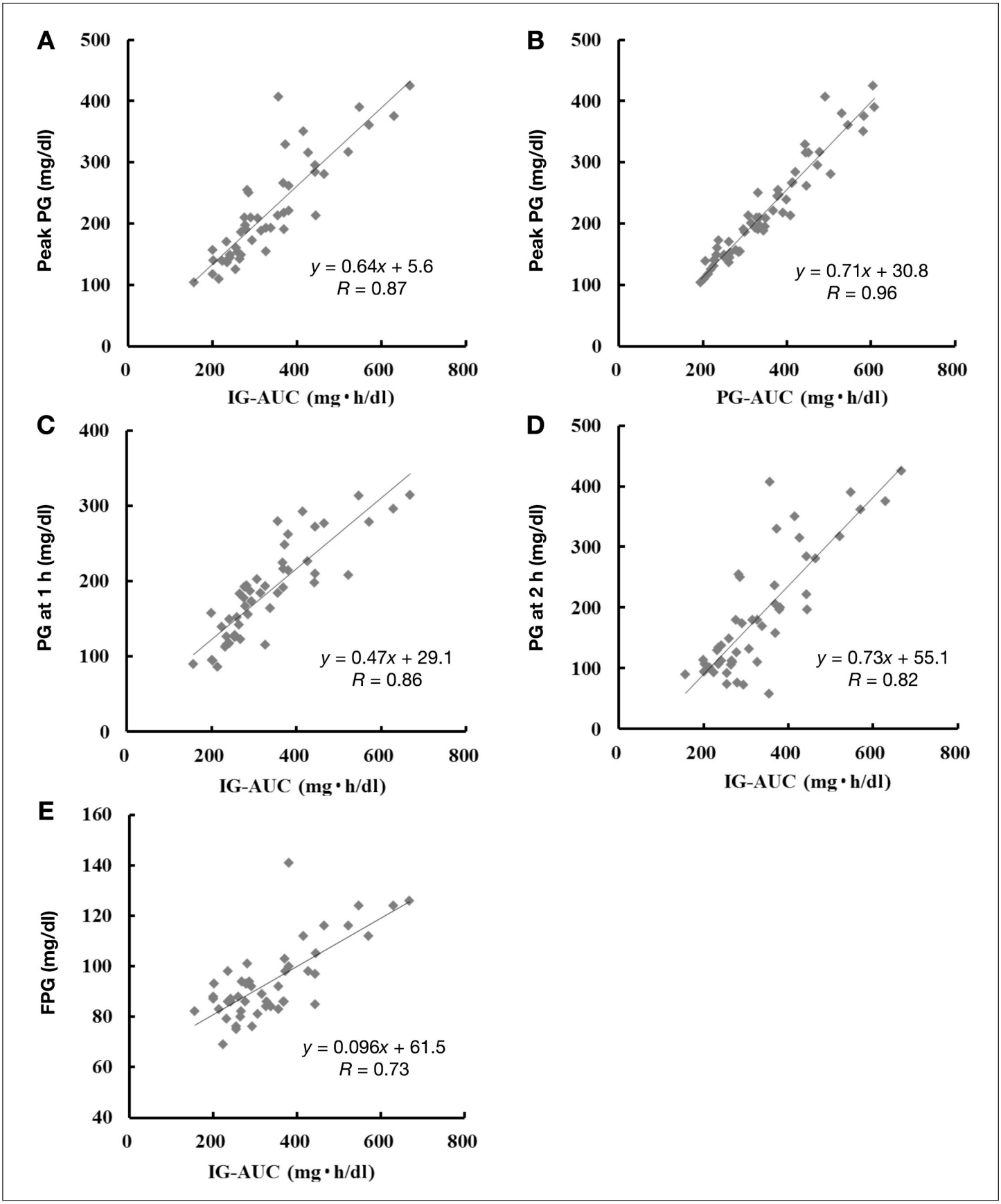

Figure 5. The correlation between **(A)** IG AUC and peak PG levels, **(B)** PG AUC and peak PG levels, **(C)** IG AUC and PG levels at 1 h, **(C)** IG AUC and PG levels at 2 h, and **(D)** IG AUC and **(E)** FPG levels. The IG AUC values are the average of two simultaneous measurements.

Discussion

We evaluated the effectiveness of sweat monitoring for precise glucose AUC measurement using MIET. However, the relatively high sweat measurement error is likely to be problematic during clinical use of this system. Therefore, we will mainly focus our discussion on the causes of frequent sweat measurement error in this study compared with that in previous studies, in addition to the adequacy of the concept of sweat monitoring and the effectiveness of this novel system.

Table 2.
Questionnaire Results[a]

Pain by	MIET	Blood Sampling
Face scale (mean ± 1SD)	1.9 ± 0.9	4.4 ± 2.3
Face scale (max)	5	10
Impression of	Hydrogel patch	Scar
No worries at all	85%	81%
Slightly uncomfortable	14%	17%
Uncomfortable	0%	2%
Very uncomfortable	2%	0%

[a] The questionnaire included questions on pain caused by the skin stamping process and venous blood sampling as well as questions on the impression left by the hydrogel patch and scarring at the stamping area. A 10-point face scale was used, in which 1 indicated minimal pain and 10 indicated maximal pain. SD, standard deviation.

Adequacy of the Concept of Sweat Detection Using Sodium Ion Level

Blood glucose estimation using IG extraction is affected by sweat glucose levels because of the low volume of glucose extracted through the skin. For example, GlucoWatch, a noninvasive glucose-monitoring system, uses iontophoresis to enhance IG extraction and provides alerts about sweat-induced measurement errors, as detected by a change in electrical conductivity of the skin during IG extraction.[17]

Our system provides alerts about possible sweat-induced errors using sodium ion levels in the hydrogel after measurement. In principle, sodium ion levels in sweat directly affect the accuracy of IG AUC measurement, because the sodium ion level is used to estimate the ISF extraction rate. If the ratio of glucose to sodium in sweat corresponded to that in blood, the influence of sweat contamination would be negligible. However, the ratio of glucose to sodium in the sweat-monitoring hydrogels varied among subjects, as shown in **Figure 6A**, consistent with findings in previous reports concerning the limitation of glucose monitoring using sweat.[18,19]

Correlations between sodium ion and glucose permeabilities for ISF and sweat are shown in **Figure 6B**. Although sodium ion permeabilities in sweat and ISF were similar, the glucose permeabilities differed and were much lower in sweat. This suggests that it is suitable to use sodium ion levels only for sweat monitoring.

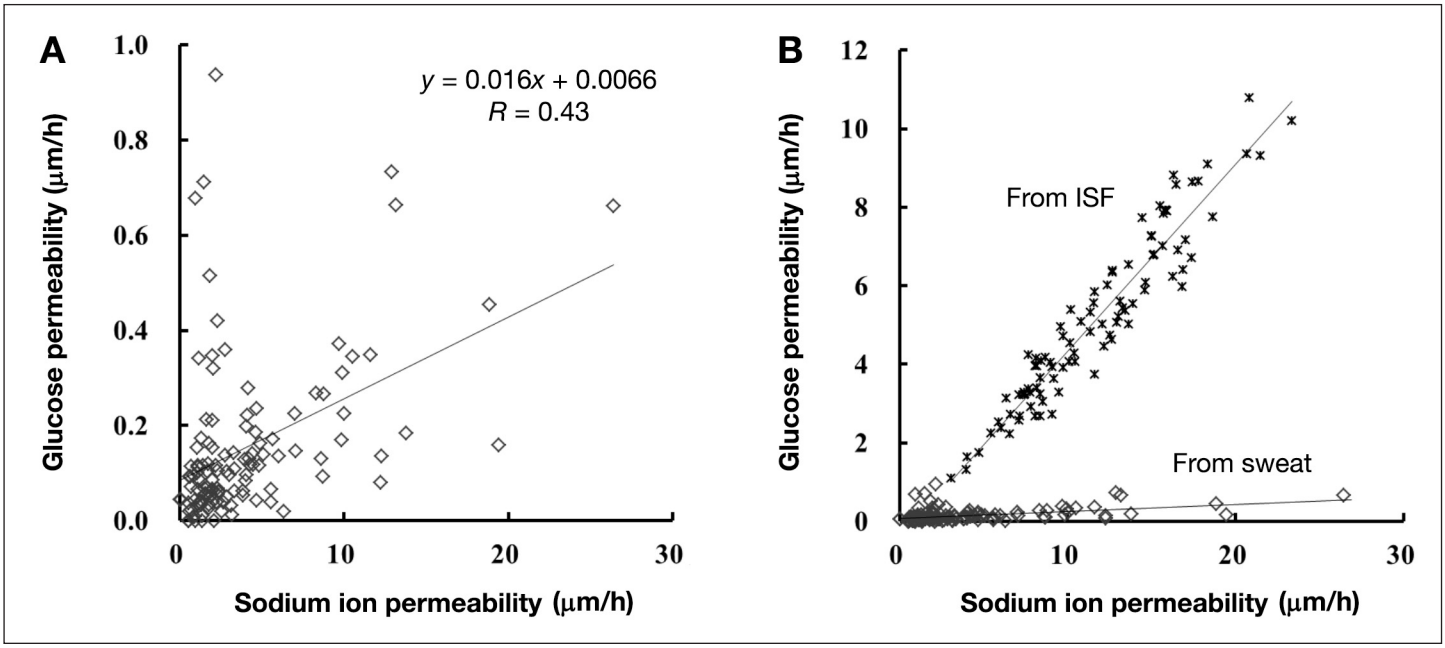

Figure 6. The correlation between sodium ion and glucose permeabilities in **(A)** the sweat patch in comparison with those in **(B)** ISF.

In this study, three parameters were suggested for detecting sweat error. In principle, sweat ratio is considered to be the key parameter for sweat error definition, because this ratio includes sodium ion levels in both ISF and sweat. A threshold level of 0.62 for the sweat ratio used in this study means that approximately 40% of the sodium ions in the hydrogel for ISF extraction were derived from sweat. Therefore, a 10% difference in sweat levels between the hydrogel for ISF extraction and that for sweat detection may cause a 4% difference in IG AUC. In this regard, if the sweat ratio is more than 0.62, data should be defined as sweat error to maintain the accuracy of IG AUC measurement.

Reduction of Sweat-Induced Error

A previous study reported no significant difference between PG AUC and IG AUC, although correction for sweat was not performed.[15] In contrast, >10% of the measurements were confounded by sweat-induced error in this study. Therefore, we investigated the differences in experimental conditions leading to these different results and identified two potential causes.

The first was the ratio of the microneedle pretreatment area to the hydrogel patch size. In the previous study, the hydrogel patch size was the same as the microneedle pretreatment area, whereas, in the present study, in order to improve the utility of hydrogel patch attachment, the area of the hydrogel patch was 1.6 times larger than that of the microneedle pretreatment area. This may have resulted in up to a 60% increase in sodium ion contamination of the hydrogel patch by sweat.

The second potential cause is the effect of seasonal variations on sweat secretion. The previous study was conducted mainly from winter to spring, whereas the present study was conducted mainly during summer. Although both trials were conducted in hospitals with controlled room temperatures of approximately 24 °C, sweat secretion may tend to increase during the summer, even at the same temperature (data not shown).

To decrease sweat-induced measurement error in all seasons, we suggest optimization of the ratio of the microneedle pretreatment area to that of the hydrogel patch size or an increase in the IG extraction rate that does not compromise the utility of the measurement process or increase patient discomfort.

Effectiveness of the Interstitial Fluid Glucose Area under the Curve Measurement

As we have previously discussed in detail,[15] glucose AUC is an accurate index of glycemic excursion after glucose loading and is widely used to monitor drug efficacy.[20,21] However, there is no well-established evidence regarding glucose AUC measurements with regard to screening for glucose intolerance or for achieving optimal levels of DM management. Therefore, further investigations must be conducted to improve this system for these purposes.

Studies using CGM have shown that glucose spikes increase the risk of diabetes complications, even with the same hemoglobin A1c levels.[22,23] It would be beneficial to be able to estimate postprandial glucose spikes without blood sampling. In the present study, we confirmed a strong correlation between PG AUC, IG AUC, and peak glucose levels over the 2 h OGTT period, which suggests the feasibility of glucose spike monitoring with our method. Further studies regarding glucose fluctuations may enhance the usefulness of IG AUC measurement using this system.

This technique could also be easily applied for longer measurement times by simply leaving the hydrogel patches on for the desired period. If the patches are placed for 4 h, AUC would reflect the total increase in postprandial glucose levels attributable to DM.[24] Glucose AUC divided by accumulation time corresponds to the average glucose level; therefore, if the patch were placed for 12 or 24 h, the average daytime, nighttime, or 1-day glucose levels could be determined without blood sampling. However, in longer AUC measurements, the sweat ratio may increase because the decrease in the ISF extraction rate is dependent on the time elapsed following microneedle application.

The ADA and the European Association for the Study of Diabetes statements have stressed the importance of personalized treatment for effective DM management.[25] To this end, precise monitoring of individual glycemic excursion is required. Our painless and easy-to-use system, which can include information on postprandial glucose

spikes and average glucose levels over extended periods, may be beneficial for the precise monitoring of an individual's glycemic status.

Lastly, we describe two possible practical issues in regard to IG AUC measurement in the clinical setting. One is the requirement for temporal control of hydrogel patch attachment. As mentioned earlier, the IG AUC measured is directly related in principle to the duration of hydrogel patch attachment. If we measure 2 h AUC, an extraction time of 2 h ± 5 min is necessary for precise measurement. The other possible issue is patient limitation in regard to IG AUC measurement. It is hypothesized that the sodium ion level in ISF is constant as an internal calibrator for IG AUC measurement. Therefore, patients with low or high serum sodium ion levels are ineligible. Further investigations are necessary to clarify patient eligibility for IG AUC measurement using our system.

Study Limitations

The robustness of the threshold level for sweat detection should be evaluated by further studies. In this study, the entire protocol was undertaken by fully trained operators only, and hence, clarification of practical issues for medical staff is required. In addition, the performance of this system should be evaluated in a home setting, because this study was conducted in a clinical setting only,

Conclusion

We confirmed the effectiveness of a sweat monitoring patch for precise AUC measurement using MIET. Our results indicated that this novel, easy-to-use AUC monitoring system is clinically useful and has potential for evaluating postprandial glucose excursion in daily DM management and clinical practice.

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Disclosures:

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