研究報文

Potential usefulness of 75-g oral glucose tolerance test using the flash glucose monitoring system in a comprehensive medical examination

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人間ドック健診におけるフラッシュグルコースモニタリングシステムを用いた75 g OGTT の可能性

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抄録

目的：本研究では，人間ドック健診におけるフラッシュグルコースモニタリングシステム（FGM）を用いた75 g 経口ブドウ糖負荷試験（OGTT）の有用性を検討することを目的とした。

方法：人間ドック健診を受診した健常ボランティア64名を対象に，FGM（FreeStyle リブレ Pro®）センサーを装着して75 g OGTT を実施した。静脈血漿血糖値（PG）は60分ごとに計3回，FGM による間質液グルコース濃度（FGM-IG）は15分ごとに計9回測定し，PG と FGM-IG の関連を検討した。

結果：PG と FGM-IG との間に有意な正の相関を認めた。FGM の精度を評価するコンセンサスエラーグリッド解析の結果，99.5 % の測定値が臨床的に利用可能とされる範囲内に該当し，平均絶対的相対的差異は13.7%であった。糖負荷前の FGM-IG は PG と比較して有意に低値であった。対象者64名中60名の OGTT において，PG と FGM-IG による判定が一致した。15分ごとの FGM-IG の測定によって，60分ごとの PG を用いた通常の OGTT では評価できないグルコース変動を捉えることが可能であった。

結論：簡便かつ侵襲少なくグルコース濃度を測定できる FGM は，75 g OGTT において有用である可能性が示唆された。

(Received 8 September, 2021, Accepted 11 November)

I. Introduction

The Japanese Society of Ningen Dock formulated a 2-day comprehensive medical examination composed of routine performed diagnostic modalities. These modalities include the 75 g oral glucose tolerance test (OGTT) for the diagnosis of diabetes or impaired glucose tolerance (IGT)[1)]. The standardized procedure of the OGTT is as follows: a baseline measurement of fasting blood glucose

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is obtained, then the patient is instructed to ingest 75 g of glucose, and repeat blood glucose measurements are performed at 1 h and 2 h after glucose administration. The OGTT primarily assesses postprandial glucose levels and observes the trends in glucose levels after glucose loading. However, the disadvantage of this test includes the inconvenience to both patient and medical staff since the test takes at least 2-h.

Continuous glucose monitoring (CGM) measures interstitial glucose levels through a cutaneous sensor[2]. One type of CGM is the flash glucose monitoring (FGM) system. Unlike other CGMs, FGM does not require calibration and displays the information using graphs and trend arrows. The FreeStyle Libre Pro® (Abbott Diabetes Care Inc., CA, USA) FGM, which continually measures interstitial glucose levels and is widely used in assessing the glycemic control of patients with diabetes as it allows convenient detection of glycemic variations[3,4].

The purpose of this study was to evaluate the difference between venous plasma glucose levels (PG) and interstitial glucose levels measured by FGM (FGM-IG) in the 75 g OGTT. Additionally, this study aimed to investigate the possibility of using FGM for the 75 g OGTT in the screening for diabetes, as a component of a comprehensive medical examination.

II. Subjects and Methods

1. Subjects

This study included 64 subjects who underwent the OGTT in a 2 day comprehensive medical examination conducted at a hospital in Kyoto from 2018 to 2019. Forty-six subjects were men and 18 were women with median ages of 51.0 and 45.5 years, respectively. Subjects with metabolic or endocrine diseases that affect glucose levels were excluded from the study. None of the subjects had received medications or other treatments.

2. Methods

On the first day of examination, the FreeStyle Libre Pro® sensor was applied on the back of each subject's upper arm between 11:00 a.m. and 1:00 p.m. On the second day, the 75 g OGTT (testing at 0, 60, and 120 min) was performed after an overnight fast (Figure 1). The FGM-IG levels were downloaded and analyzed using the FreeStyle Libre® software.

The subjects were classified into three groups according to the criteria of the Japan Diabetic Society[5]: (1) diabetes mellitus (DM) type, with a fasting PG level ≥ 126 mg/dL and/or 120 min level ≥ 200 mg/dL; (2) normal glucose tolerance (NGT) type, with a fasting PG level < 110 mg/dL and 120 min level < 140 mg/dL; and (3) impaired fasting glucose (IFG)/IGT type, with a fasting PG level of 110-125 mg/dL and/or 120 min level of 140-199 mg/dL.

Additionally, height, body weight, waist circumference (WC), and fasting blood indices (HbA1c and insulin) were measured. Body mass index (BMI) was calculated by dividing body weight (kg) by the square of the subject's height (m). Furthermore, the homeostasis model assessment of insulin resistance (HOMA-IR) was calculated as fasting serum glucose multiplied by fasting insulin then divided by 405[6].

As an index of excursion during the OGTT, the area under the curve (AUC) of FGM-IG and PG were calculat-

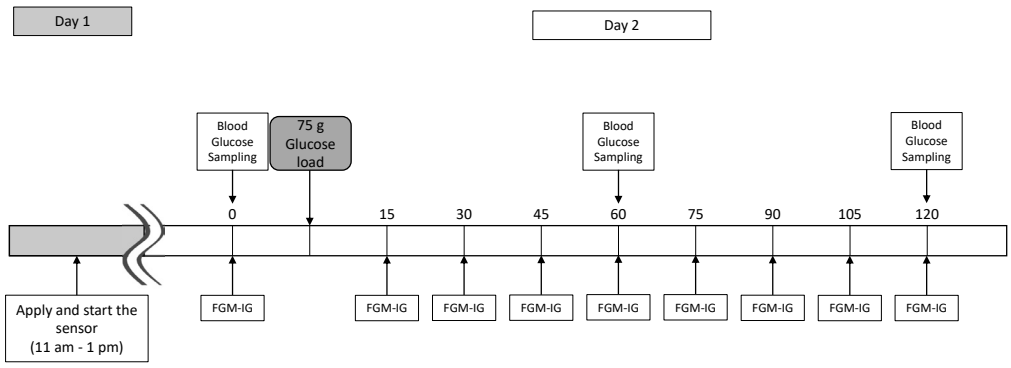


Figure. 1 Study design

ed.

We compared FGM-IG and PG levels using consensus error grid analysis[7, 8], which is an accepted tool for the clinical accuracy of blood glucose. Additionally, the mean absolute relative difference (MARD) of FGM was calculated as a parameter to characterize FGM performance[8-10].

To assess the factors affecting the MARD and a diagnosis in the OGTT using FGM-IG, subjects were classified according to the presence or absence of concordant diagnosis using PG and FGM-IG.

Subjects were stratified into tertiles based on the accumulated volumes of the MARD to investigate the relationship between the MARD and metabolic parameters.

3. Statistical analysis

Data were analyzed using IBM SPSS version 25 (IBM Corp. NY, USA). The Mann-Whitney U test was used to assess significant differences between the two groups and the Kruskal-Wallis test was used to assess significant differences between the three groups for continuous variables. Fisher's exact test was used to assess significant differences in the categorical variables. Spearman's correlation coefficient was used to assess the relationship between two parameters. Wilcoxon signed-rank test was used to assess significant differences between matched samples. Data are presented as the median (first quartile, third quartile). Statistical significance was set at $P < 0.05$.

4. Ethical statement

This study was approved by the Research Ethics Committee of Kyoto Women's University (Approval number 29-19) and was performed according to the guidelines of the Declaration of Helsinki. Written informed consent was obtained from all subjects.

III. Results

Subject characteristics are shown in Table 1. Among the clinical parameters, BMI, WC, PG (0, 60, 120 min), FGM-IG (60 min), and AUC of FGM-IG and PG were significantly higher in men than in women.

A significant relationship was found between the PG and FGM-IG levels in 192 PG analysis conducted simultaneously with FGM-IG ($y = 0.949x + 2.063$, $r = 0.841$, $P < 0.001$) (Figure 2). The consensus error grid analysis showed that the percentages of levels within Zone A (no effect on clinical action) and B (altered clinical action-little or no effect on clinical outcome) against PG were 99.5 %. Furthermore, the MARD was 13.7 %.

Figure 3 shows the difference between FGM-IG and PG at 0, 60, and 120 min. At 0 min, FGM-IG levels were significantly lower than PG levels; however, no significant differences were observed at 60 and 120 min.

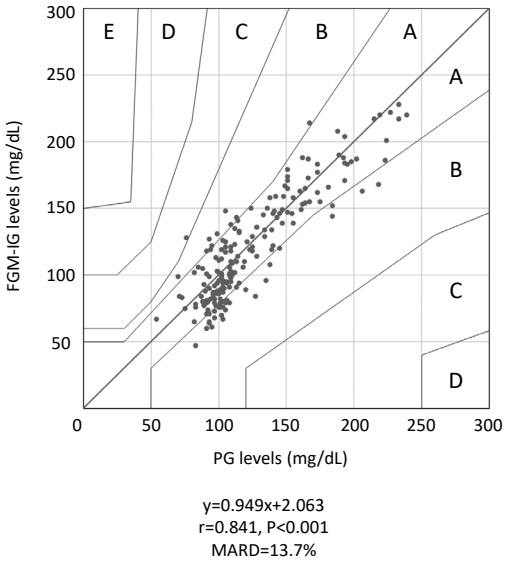
Table 1. Subject characteristics

		Male (n = 46)	Female (n = 18)	P	
Age	years	51.0 (43.0, 55.0)	45.5 (30.0, 52.5)	0.076	
BMI	kg/m^2	23.0 (21.4, 25.1)	19.3 (18.0, 22.8)	0.001	*
WC	cm	84.0 (81.0, 89.3)	72.3 (67.8, 84.4)	0.001	*
PG (0 min)	mg/dL	101.5 (97.0, 106.0)	96.5 (91.8, 100.3)	0.011	*
(60 min)	mg/dL	165.0 (138.0, 192.3)	114.5 (90.3, 156.5)	0.002	*
(120 min)	mg/dL	119.5 (102.0, 145.5)	107.0 (86.5, 116.5)	0.043	*
FGM-IG (0 min)	mg/dL	87.5 (79.0, 94.0)	81.0 (74.8, 87.8)	0.117	
(60 min)	mg/dL	160.5 (145.8, 186.3)	126.0 (102.5, 150.8)	0.001	*
(120 min)	mg/dL	121.5 (106.0, 146.0)	109.5 (95.5, 125.8)	0.117	
Insulin (0 min)	μU/mL	6.1 (3.8, 8.0)	4.9 (3.5, 7.7)	0.464	
(60 min)	μU/mL	52.0 (30.3, 88.0)	45.1 (26.4, 61.9)	0.263	
(120 min)	μU/mL	46.4 (29.1, 60.7)	42.8 (25.7, 60.5)	0.737	
FGM-IG AUC	mg/dL・min	15960.0 (14550.0, 18810.0)	12960.0 (10905.0, 15232.5)	0.001	*
PG AUC	mg/dL・min	15825.0 (14355.0, 18015.0)	13215.0 (11160.0, 14655.0)	0.001	*
HbA1c	%	5.7 (5.4, 5.7)	5.4 (5.3, 5.7)	0.051	
HOMA-IR		1.5 (0.9, 2.0)	1.1 (0.9, 1.8)	0.335	

Mann-Whitney test

Data are expressed as median (first quartile, third quartile).

BMI: Body mass index, WC: Waist circumference, PG: Plasma glucose, FGM-IG: Interstitial glucose levels measured by the flash glucose monitoring system, AUC: Area under the curve, HOMA-IR: Homeostasis model assessment for insulin resistance



Zone	Risk
A	no effect on clinical action
B	altered clinical action—little or no effect on clinical outcome
C	altered clinical action—likely to affect clinical outcome
D	altered clinical action—could have significant medical risk
E	altered clinical action—could have dangerous consequences

Figure 2. Consensus error grid analysis

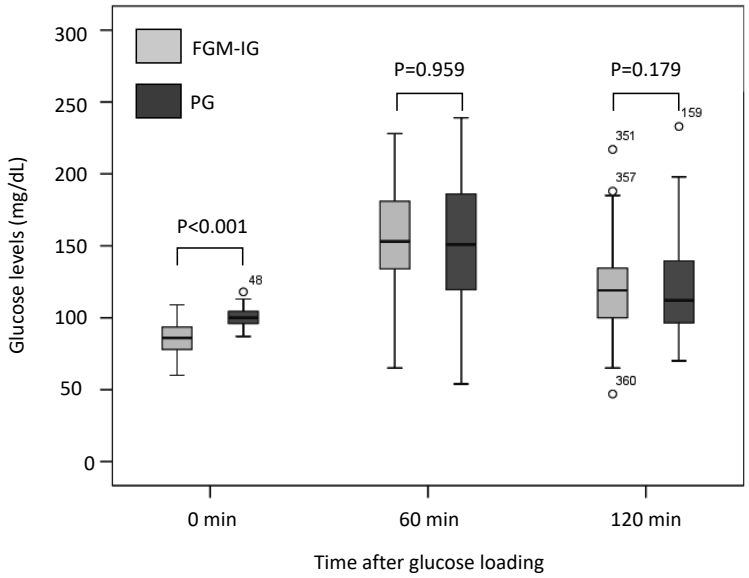


Figure 3. Comparison between levels of FGM-IG and PG

Table 2. Diagnosis using PG and FGM-IG

		PG		
		NGT	IFG/IGT	DM
FGM-IG	NGT	46	4	0
	IFG/IGT	0	13	0
	DM	0	0	1

PG: Plasma glucose level, FGM-IG: Interstitial glucose levels measured by the flash glucose monitoring system, NGT: Normal glucose tolerance, IFG: Impaired fasting glucose, IGT: Impaired glucose tolerance, DM: Diabetes mellitus

Table 2 shows the diagnosis of diabetes using PG and FGM-IG in the OGTT. Among 64 subjects, a concordant diagnosis between FGM-IG and PG was established in 60 subjects. Four subjects were diagnosed with IFG/IGT using PG levels and NGT using FGM-IG levels. These four subjects were all male and had a BMI ≥ 25 kg/m^2, WC ≥ 85 cm, and high HOMA-IR.

Table 3 shows the relationship between the MARD and metabolic parameters stratified by the MARD. In WC, the second tertile of the MARD was significantly lower than the first tertile of the MARD (P = 0.044). Regarding PG levels (0 and 120 min), the third tertile of the MARD was significantly lower than the first tertile of the MARD (P = 0.013 and P < 0.001, respectively).

Figure 4 shows the trend of glucose levels of three subjects during the OGTT. These three subjects had similar characteristics in BMI, WC, HbA1c, and HOMA-IR. They were diagnosed with NGT based on PG; however, glucose trends observed using FGM-IG showed different patterns for each patient.

IV. Discussion

In this study, we evaluated the utility of the 75 g OGTT using FGM as a screening procedure for diabetes. The

Table 3. Relationship between the MARD and metabolic parameters

		T1 (n = 21)	T2 (n = 22)	T3 (n = 21)	P	
Sex	Male (%)	18 (85.7)	16 (72.7)	12 (57.1)	0.124	
Age	years	52.0 (38.5, 56.0)	51.0 (44.0, 53.5)	46.0 (40.0, 53.0)	0.361	
BMI	kg/m^2	22.7 (21.0, 25.0)	22.5 (18.7, 23.9)	22.3 (19.9, 25.2)	0.384	
WC	cm	84.0 (81.3, 90.5)	79.8 (69.5, 84.6)	84.0 (74.3, 88.3)	0.044	T1 vs T2
PG (0 min)	mg/dL	103.0 (97.5, 109.0)	100.0 (97.0, 103.3)	97.0 (92.0, 101.5)	0.013	T1 vs T3
(60 min)	mg/dL	166.0 (137.0, 194.0)	157.5 (127.3, 181.8)	128.0 (99.5, 175.5)	0.155	
(120 min)	mg/dL	139.0 (114.5, 153.0)	109.0 (101.0, 135.5)	94.0 (82.5, 117.5)	<0.001	T1 vs T3
Insulin (0 min)	μU/mL	5.7 (3.9, 7.1)	5.3 (3.3, 8.1)	6.0 (4.6, 8.3)	0.467	
(60 min)	μU/mL	44.5 (27.9, 91.1)	47.9 (28.8, 55.2)	51.1 (30.9, 96.1)	0.659	
(120 min)	μU/mL	51.0 (32.3, 64.4)	41.2 (26.6, 60.8)	33.2 (25.8, 53.9)	0.433	
HbA1c	%	5.6 (5.3, 5.9)	5.7 (5.4, 5.8)	5.5 (5.4, 5.7)	0.452	
HOMA-IR		1.4 (1.0, 1.9)	1.4 (0.7, 2.0)	1.4 (1.0, 2.0)	0.664	

Fisher's exact test, Kruskal-Wallis test

Data are expressed as median (first quartile, third quartile), or number (percentage).
BMI: Body mass index, WC: Waist circumference, PG: Plasma glucose,
HOMA-IR: Homeostasis model assessment for insulin resistance

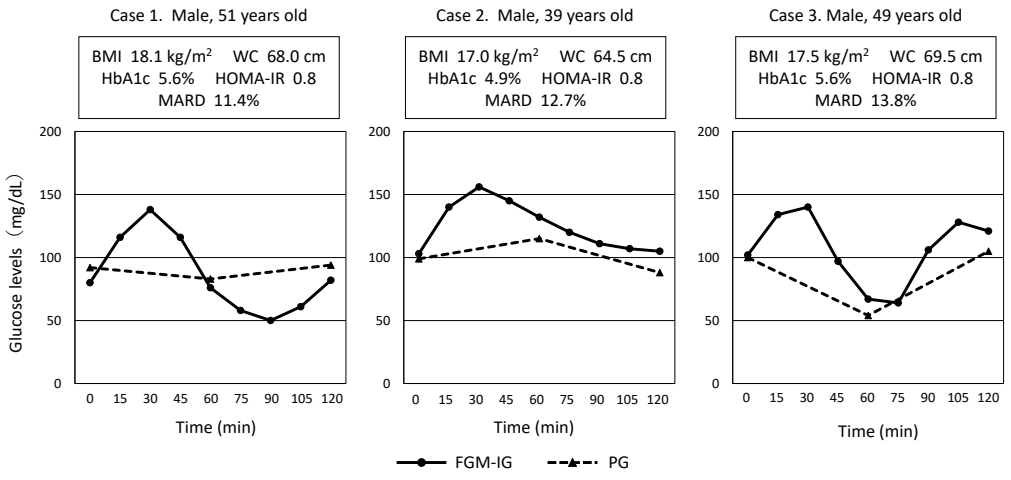


Figure 4. Cases of glucose fluctuation during the OGTT in subjects with NGT

consensus error grid analysis of glucose levels measured by FGM with PG as references showed that 99.5 % of measurements by FGM were classified as zones A and B; furthermore, the MARD was 13.7 %. These results suggest the viability of the OGTT using FGM as a screening test for diabetes as part of a comprehensive medical examination. This is the first reported evaluation of the potential usefulness of the OGTT using FGM in a comprehensive health examination.

FGM is unique among existing interstitial glucose monitoring technologies as it utilizes a wired enzyme factory that only requires calibration every 14 days[3] and has the capacity to obtain interstitial glucose every 15 min. Additionally, FGM is easy to perform and the patient experiences no pain or discomfort when it is administered on the upper arm. Furthermore, they are able to perform normal daily activities after the procedure, including free movement, bathing, and swimming[11]. Several studies have shown the effectiveness of FGM in evaluating glycemic control while minimizing pain and maintaining the quality of life of patients[12].

Generally, screening tests, such as health check-ups, are preferably non-invasive and non-cumbersome to subjects. In the OGTT recommended by the Japanese Society of Ningen Dock, three rounds of blood drawing (0, 60, and 120 min) are required. On the other hand, FGM can measure glucose levels in nine occurrences (0, 15, 30, 45, 60, 75, 90, 105, and 120 min) during the OGTT to assess the trend of glucose levels without the need for blood sampling. A detailed analysis of the trends of glucose levels is useful in the health management of subjects. Furthermore, the utility of FGM in improving the lifestyle of subjects is maximized when the sensor is continuously worn for 14 days after the OGTT; while daily life is maintained, the relationship between FGM-IG and daily life is also established.

This study was performed during a 2 day comprehensive medical examination. The glucose levels recorded on the first 2 days of use of FGM are known to be not entirely precise. However, our study revealed that among 192 pairs of samples, 191 pairs were classified in zones A and B; therefore, the accuracy of glucose level measurements using overnight FGM will exhibit stability to some extent. Additionally, one study found no difference in results when the first 2 days of FGM were excluded from their analysis[13].

We found that FGM-IG levels were significantly lower than the PG levels only at 0 min of the OGTT; additionally, FGM might be underestimated when blood glucose levels are low. A previous study reported that glucose levels measured by FGM were lower than the glucose levels in the venous or capillary blood of patients with diabetes[14, 15]. Meanwhile, Sekido *et al.* found that individual validations tended to be significantly higher in FGM-IG than in PG in seven healthy volunteers[16]. This may reflect sensor-dependent delays or a 4-10 min lag between interstitial and venous readings[17-19]; this time lag should be considered when using FGM.

In the comparison between diagnosis by PG and FGM-IG, the diagnosis was concordant in 93.8 % of the subjects. Four of the 64 subjects were diagnosed with IFG/IGT based on PG and NGT using FGM-IG, and these subjects were obese men with insulin resistance. Therefore, careful evaluations are required for such subjects.

Two factors, namely WC and PG levels (0 and 120 min), were associated with deviations between PG and FGM-IG levels. A previous study reported that patient characteristics, including age and sex, had no effect on the accuracy of the method[3]. Yoshino *et al.*[20] reported that the MARD in FGM levels was affected by BMI and PG (0 min). Another study reported that the accuracy of FGM depended on the content of subcutaneous tissue at the location where the sensor was inserted. FGM estimates interstitial glucose levels through a cutaneous sensor with a soft needle; therefore, the position of the needle head may be related to the levels of glucose using FGM[21]. In this study, the effects of WC and PG (0 and 120 min) on the MARD in FGM-IG levels were not identified; however, a previous study found that body composition, including visceral fat and low PG, may affect the MARD[22]. The absolute levels of FGM-IG are not generally accepted diagnostic substitute for PG levels, especially levels may be underestimated when blood glucose is relatively low. However, FGM may be a clinically acceptable screening modality if its limitations are well-understood[23]. Moreover, in the OGTT, FGM not only assesses glucose levels but also provides detailed information regarding glucose trends. For example, in cases 1 and 3, in Figure 4, PG levels were estimated every 60 minutes, whereas FGM-IG levels were estimated every 15 minutes. In these cases, the detection of changes in glucose levels via FGM

suggest the possibility of reactive hypoglycemia. It will be necessary to comply with new criteria for use of FGM-IG in OGTTs for diabetes screening. FGM is widely used and non-invasive; however, the device is relatively expensive, and the procedure is not easily adaptable to health examinations. Although, the cost is expected to decrease in the near future.

This study has some limitations. First, FGM measures interstitial glucose levels and not blood levels. Further research is needed to investigate the difference between FGM-IG and PG levels. Second, the MARD was calculated only during the OGTT, which is a glucose loading test. Third, as the number of subjects was small, we were unable to examine the results by sex. Finally, there were individual differences in FGM-IG. It is necessary to increase the sample size in the future for further analysis.

V. Conclusions

OGTTs using an FGM sensor may be a potential screening test for diabetes as a component of a comprehensive medical examination, provided that the limitations of FGM are understood. FGM can screen subjects with IGT and diabetes, and identify the detailed glucose trends in subjects with minimal pain. Furthermore, it has the potential to provide health guidance and improve subjects' lifestyles when continuously worn after an OGTT. Further investigation is needed to evaluate the accuracy of glucose levels using FGM and to account for the differences between FGM-IG and PG levels.

Acknowledgments

We thank the staff of the health check-up center at Rakuwakai Toji Minami Hospital.

Conflict of Interest

We received funding from the Japanese Society of Ningen Dock.

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