

**Protocol version 1.5
(English translation)**

**Patient-Driven lifestyle
modification using FreeStyle
Libre in patients with type 2
diabetes: The PDF study**

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Hun Jee Choe, Eun-Jung Rhee

Jong Chul Won, Young Min Cho

Table of contents

Proccol synopsis	2
I. Background	5
II. Study Objective	6
III. Study Endpoints	6
<input type="checkbox"/> Primary Outcome Measures:	6
<input type="checkbox"/> Secondary Outcome Measures:	6
<input type="checkbox"/> Other Endpoints:	7
IV. Study Population	8
V. Study Eligibility	8
<input type="checkbox"/> Inclusion Criteria	8
<input type="checkbox"/> Exclusion Criteria	9
VI. Sample Size	10
VII. Study Design	10
<input type="checkbox"/> Intervention Group	11
<input type="checkbox"/> Control Group	12
VIII. Study Devices and Materials	13
<input type="checkbox"/> General Education for Diabetes Care	13
<input type="checkbox"/> Korean Version of Revised Summary of Diabetes Self-Care Activities Questionnaire	14
<input type="checkbox"/> FreeStyle Libre CGM	16
<input type="checkbox"/> SEOUL Algorithm	16
<input type="checkbox"/> PDF CGM Diary	18
<input type="checkbox"/> BGM Devices	20
IX. Data Collection and Management	21
X. Statistical Considerations	21
XI. Adverse Events	23
<input type="checkbox"/> Anticipated Adverse Effects	23
<input type="checkbox"/> Unanticipated Adverse Effects	24
XII. References	25

Protocol Synopsis

Title	Patient-Driven lifestyle modification using FreeStyle Libre in type 2 diabetes patients: The PDF study
Principal Investigator	Young Min Cho, Department of Internal Medicine, Seoul National University College of Medicine
Sponsor	Daewoong Pharmaceuticals Co., Ltd.

Study Objective	To assess the effect of patient-driven lifestyle modification using intermittent CGM in type 2 diabetes mellitus patients who are not on intensive insulin regimen
Study Design	Multicenter, randomized, open-label, controlled study
Study Devices	FreeStyle Libre CGM (Abbott Diabetes Care®, Witney, Oxon, UK); SEOUL algorithm; Blood glucose meter (FreeStyle Optimum Neo, Abbott Diabetes Care®, Witney, Oxon, UK)
Study Endpoints	<ul style="list-style-type: none"> ● <u>Primary Outcome Measures:</u> <ul style="list-style-type: none"> ✓ Change in HbA1c Between group differences (CGM and BGM) for the change in HbA1c from baseline to month 3 ● <u>Secondary Outcome Measures:</u> <ul style="list-style-type: none"> ✓ Change in mean fasting glucose Between group differences (CGM and BGM) for the change in fasting glucose from baseline to month 3 ✓ Change in body weight Between group differences (CGM and BGM) for the change in body weight from baseline to month 3 ✓ Change in systolic blood pressure Between group differences (CGM and BGM) for the change in blood pressure from baseline to month 3 ✓ Change in waist circumference Between group differences (CGM and BGM) for the change in waist circumference from baseline to month 3 ✓ Change in lipid level

	<p>Between group differences (CGM and BGM) for the change in lipid level (total cholesterol, triglycerides, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol) from baseline to month 3</p> <p>✓ Change in the Korean Version of Revised Summary of Diabetes Self-Care Activities Questionnaire (SDSCA-K) survey score</p> <p>Between group differences (CGM and BGM) for the change in survey score from baseline to month 3</p>
Study Population	Adults with type 2 diabetes mellitus who are currently not on intensive insulin regimen, with or without oral anti-diabetic therapy, and/or GLP-1 analogue injections, and/or basal insulin, suboptimally controlled
Study Sites	<p>Three sites from Seoul, Republic of Korea that possess research capabilities and have clinicians in the research site experienced in interpreting CGM and BGM data</p> <ul style="list-style-type: none"> ✓ Seoul National University Hospital ✓ Inje University Sanggye Paik Hospital ✓ Sungkyunkwan University Kangbuk Samsung Hospital
Study Overview	<p>This study is referred to as the "Patient-Driven lifestyle modification using FreeStyle Libre in type 2 diabetes patients", also known as the PDF study.</p> <p>It will assess potential benefits of using Continuous Glucose Monitoring (CGM) versus Blood Glucose Monitoring (BGM) when combined with personalized education on lifestyle modification in people with type 2 diabetes. Specifically, we will investigate patients who have an elevated HbA1c between 7.0–10.0% who are not using prandial insulin.</p> <p>Potential participants will be screened from routine outpatient clinic visits, will be randomized to either the CGM or BGM group in a 1:1 ratio. Participants from both groups will receive education on lifestyle modification and will be reminded every 4 weeks with structured phone visits. Study will be completed at the visit on 12 weeks of follow up with the same laboratory examinations (including HbA1c) and survey from the baseline.</p>

I. Background

Type 2 diabetes mellitus (T2D) is a chronic complex disease that requires continuous treatment and management. Among multifaceted aspects of glycemic control, behavior and lifestyle modification are the cornerstones of successful treatment. In the previous Lifestyle Over and Above Drugs in Diabetes (LOADD) study, intensive individualized dietary advice was advantageous in improving HbA1c in patients with T2D with unsatisfactory glycemic control (1). Postprandial glycemic response was more predictable, however, when personalized approach was applied that considered a variety of characteristics of the individuals, then when merely total calories or carbohydrate counting was applied (2).

Ideally, dietary advice should be precisely tailored to embrace the complex postprandial responses according to individual food consumption and phenotype (3; 4). Blood glucose monitoring (BGM) enables assessment of glycemic patterns in response to medical nutritional therapy. Even in patients with T2D who are not on insulin regimen, BGM has proved to be efficacious if integrated into a collaborative program of structured care (5; 6). Nevertheless, anxiety and pain that arise from finger pricking are not negligible, and even frequent BGM cannot fully capture glycemic fluctuations completely and may fail to detect asymptomatic or nocturnal hypoglycemia.

Continuous glucose monitoring (CGM) provides robust information on glycemic control that may be overlooked by BGM (7). The advent of CGM has empowered patients and healthcare providers to appraise glycemic patterns comprehensively and incorporate individual glycemic responses to diet and physical activities (8). The MOBILE study group recently affirmed benefits of real time CGM in patients with T2D on basal insulin (9; 10). However, data on whether intermittently scanned CGM (isCGM) is equally advantageous to patients with T2D who do not use prandial insulin are scarce.

Since isCGM necessitates the user to deliberately scan the sensor to obtain glucose data, we presumed that clinical benefit would be maximized when motivated patients are trained with structured algorithm which can be individually customized. Thus, we proposed a new algorithm that facilitates lifestyle changes from the scanned glucose data through immediate feedback: the Self-Evaluation Of Unhealthy foods by Looking at postprandial glucose levels (SEOUL) algorithm. Here we aimed to see the effect of patient-driven lifestyle modification using isCGM in T2D patients who are not on intensive insulin regimen.

II. Study Objective

To assess the effect of patient-driven lifestyle modification using intermittent CGM in type 2 diabetes mellitus patients who are not on intensive insulin regimen

III. Study Endpoints

- **Primary Outcome Measures:**

- ✓ **Change in HbA1c**

Between group differences (CGM and BGM) for the change in HbA1c from baseline to month 3

- **Secondary Outcome Measures:**

- ✓ **Change in mean fasting glucose**

Between group differences (CGM and BGM) for the change in fasting glucose from baseline to month 3

✓ **Change in body weight**

Between group differences (CGM and BGM) for the change in body weight from baseline to month 3

✓ **Change in systolic blood pressure**

Between group differences (CGM and BGM) for the change in blood pressure from baseline to month 3

✓ **Change in waist circumference**

Between group differences (CGM and BGM) for the change in waist circumference from baseline to month 3

✓ **Change in lipid level**

Between group differences (CGM and BGM) for the change in lipid level (total cholesterol, triglycerides, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol) from baseline to month 3

✓ **Change in the Korean Version of Revised Summary of Diabetes Self-Care Activities Questionnaire (SDSCA-K) survey score**

Between group differences (CGM and BGM) for the change in survey score from baseline to month 3

● **Other Endpoints:**

Exploratory analyses will be performed on the outcomes listed below to better understand the

effect of CGM and the SEOUL algorithm.

✓ **Total population**

- ✓ Percent reaching HbA1c of <6.5% (48 mmol/mol), <7.0% (53 mmol/mol), <7.5% (58 mmol/mol), <8.0% (64 mmol/mol), <8.5% (69 mmol/mol), <9.0% (75 mmol/mol), <9.5% (80 mmol/mol), and <10.0% (86 mmol/mol) at month 3
- ✓ Percent decreasing HbA1c by 0.5% or more (absolute)
- ✓ Insulin users: Insulin dose from baseline to month 3

✓ **Intervention group**

- ✓ Time in the target range (TIR) of 70–180 mg/dL, time above the target range (TAR, > 180 mg/dL and > 250 mg/dL), time below the target range (TBR, < 70 mg/dL and < 54 mg/dL), coefficient of variation (%CV) at baseline and at month 3
- ✓ TIR, TAR, TBR, %CV, and mean glucose for CGM 1–6

IV. Study Population

Adult type 2 diabetes patients who are currently not on intensive insulin regimen, with or without oral anti-diabetic therapy, and/or GLP-1 analogue injections, and/or basal insulin, suboptimally controlled

V. Study Eligibility

● **Inclusion Criteria**

- ✓ Age between 19–80

- ✓ Able to understand instructions in Korean language
- ✓ Diagnosed with type 2 diabetes
- Fasting blood glucose ≥ 126 mg/dL or
- HbA1c $\geq 6.5\%$ or
- Type 2 diabetes by clinical history and treated with antidiabetic medications of lifestyle modifications
- ✓ HbA1c of 7.0–10.0% within 3 months
- ✓ Stable medication regimen during the 3 months prior to entry visit
- ✓ Naïve to intermittent CGM and willing to participate in the study

● **Exclusion Criteria**

- ✓ Type 1 diabetes patients
- ✓ Use of short acting insulin in the 3 months prior to entry visit or planning to initiate prandial insulin or short acting insulin
- ✓ Pregnancy at time of screening or are planning to become pregnant during the study
- ✓ Alcoholics or addicted to drugs
- ✓ Heavy smokers of nicotinic acid ≥ 1500 mg/day
- ✓ Use of glucocorticoid or other medications that will affect glycemic control (including immunosuppressants such as cyclosporine, tacrolimus, sirolimus)
- ✓ Taking obesity drugs (Orlistat, phentermine, phentermine/topiramate, naltrexone/bupropion, liraglutide 3.0 mg [participation is permitted if the patient is taking 1.8 mg or less of liraglutide as an antidiabetic drug and not for the purpose of

weight reduction])

- ✓ Sever liver disease that may compromise patient safety
- ✓ End-stage renal stage on dialysis
- ✓ Acute perioperative period or planning to go through surgery with general anesthesia during the study period
- ✓ Known allergy to medical grade adhesives or any other skin problems that may interfere with CGM sensor insertion (burn, hypertrichosis, inflammation, urticaria, tattoo)
- ✓ Inapt to participate in the study made at the investigator's discretion

VI. Sample Size

A sample size was calculated to detect a difference in HbA1c with 80% power if the true difference between the group is at least 0.35% with the standard deviation of 0.65% (11-14). With the 2-sided $\alpha = 0.05$ and dropout rate of 10%, 63 participants were required for each group.

VII. Study Design

This is a multicenter, randomized, open-label, controlled study without a run-in period. Targeted participants will be recruited from the investigator team's diabetes and endocrine practice through routine outpatient clinic.

After providing consent, all potential participants will be assessed for eligibility. Anthropometric measures including height, weight, waist circumference, blood pressure will

be measured, and medical history will be reviewed. Screening labs include fasting plasma glucose, HbA1c, aspartate aminotransferase, alanine aminotransferase, blood urea nitrogen, serum creatinine, estimated glomerular filtration rate, total cholesterol, triglyceride, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol. If all the screening labs are performed within two weeks from the entry visit, repeat labs may be omitted

All participants will receive general diabetes education sessions, conduct the Korean Version of Revised Summary of Diabetes Self-Care Activities Questionnaire (SDSCA-K) survey, and will subsequently be randomized into the intervention group or the control group using the permuted block design with the block size of 4 and 6 generated by an independent nurse not involved in the study.

- **Intervention Group**

- ✓ A LibreLink app will be installed on participant's smart phone.
- ✓ A LibreView account will be set up and linked to the research site.
- ✓ The first FreeStyle Libre CGM device (Abbott Diabetes Care®, Witney, Oxon, UK) will be inserted at the study site by the registered nurse.
- ✓ During the 60-minute warm up after applying the sensor, the patient will receive the education on applying the FreeStyle Libre CGM sensor, scanning, and interpreting CGM readings.
- ✓ Structured instruction on SEOUL algorithm will be provided. A detailed explanation of the SEOUL algorithm is described below. A PDF CGM Diary created by the PDF study team will be provided to record daily glucose assessment.
- ✓ Participants will be provided with 6 additional FreeStyle Libre CGM devices to use

during the 3 months study period, with one provided as a surplus in case a sensor accidentally falls off before the 14-day expiry date. Any unused sensors are to be returned at the end of the study period.

- **Control Group**

- ✓ Participants in the control group will be provided with a blood glucose meter (FreeStyle Optimum Neo, Abbott Diabetes Care®, Witney, Oxon, UK), lancets, glucose test strips sufficient for BGM twice daily.
- ✓ Logbook created by the PDF study team will be given to record blood sugar.

During the study period, the registered nurse will make phone/remote contacts every four weeks to encourage both the intervention group and the control group to continue the lifestyle modification. Changes in oral diabetes medication will not be made during the study period unless deemed clinically warranted by study clinician. Basal insulin users who are accustomed to insulin titration are allowed to adjust insulin dose accordingly. Participants in the intervention group could discuss any device issues requiring troubleshooting with the research nurse (the research coordinator) during the study period, but no therapy changes will be recommended except for safety issues.

At the end of the month 3, participants will visit the clinic and blood will be drawn for fasting plasma glucose, HbA1c, aspartate aminotransferase, alanine aminotransferase, blood urea nitrogen, serum creatinine, estimated glomerular filtration rate, total cholesterol, triglyceride, high-density lipoprotein cholesterol, low-density lipoprotein cholesterol. SDSCA-K survey will be repeated to monitor the behavior change in diabetes self-management.

For participants who have completed the visit 1 (V1) and the visit 2 (V2) with blood labs and SDSCA-K surveys, 『The Personalized Diet: The Pioneering Program to Lose Weight and

Prevent Disease』 (ISBN: 9791159431562(1159431566)) by Eran Segal available in Korean translation will be given as reimbursement. Financial reimbursement of \$20 and \$30 will be given for participants completing V1 and V2, respectively.



Figure 1 Study Design Diagram

VIII. Study Devices and Materials

● General Education for Diabetes Care

Participants in both the intervention group and the control group will receive general education for diabetes self-management using the materials that the PDF study team has created, as well as movie clips provided by Korean Diabetes Association (KDA).

1. KDA video: Nutrition

https://m.diabetes.or.kr/bbs/Movie_view.php?code=edu_movie&number=1024#

2. KDA video: Physical activity

https://m.diabetes.or.kr/bbs/Movie_view.php?code=edu_movie&number=1043

3. KDA video: Resistance exercise

https://m.diabetes.or.kr/bbs/Movie_view.php?code=edu_movie&number=1044

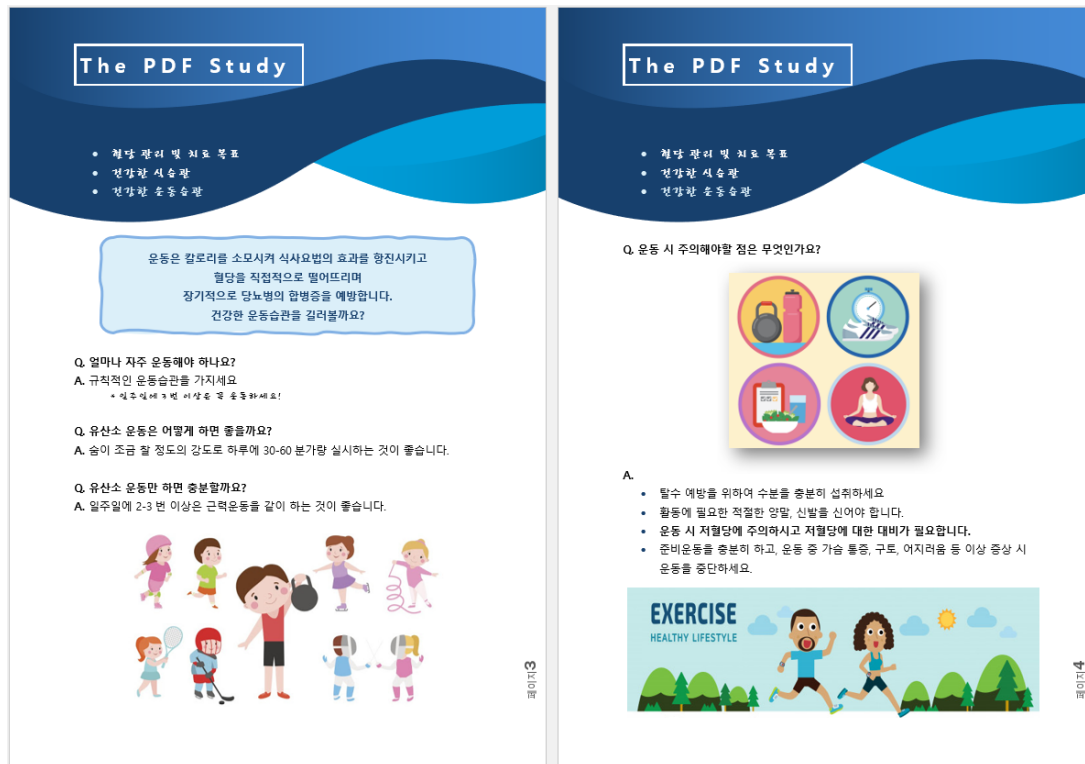


Figure 2 Education material for all participants

This self-created material provides general information for patients with type 2 diabetes regarding behavior and lifestyle modifications based on the most recent American Diabetes Association recommendations.

● Korean Version of Revised Summary of Diabetes Self-Care Activities Questionnaire (SDSCA-K)

Participants were asked to take the SDSCA-K survey before randomization and at V2. All questions were translated and provided in Korean language.

The Revised Summary of Diabetes Self-Care Activities (SDSCA-K)

※ The questions below ask you about your diabetes self-care activities during the past 7 days. If you were sick during the past 7 days, think back to the last 7 days that you were not sick.

Item	
	How many of the last SEVEN DAYS have you followed a healthful eating plan?
	0 1 2 3 4 5 6 7
Diet	On average, over the past month, how many DAYS PER WEEK have you followed your eating plan?
	0 1 2 3 4 5 6 7
	On how many of the last SEVEN DAYS did you eat five or more servings of fruits and vegetables?
	0 1 2 3 4 5 6 7
Exercise	On how many of the last SEVEN DAYS did you participate in at least 30 minutes of physical activity? (Total minutes of continuous activity, including walking).
	0 1 2 3 4 5 6 7
	On how many of the last SEVEN DAYS did you participate in a specific exercise session (such as swimming, walking, biking) other than what you do around the house or as part of your work?
	0 1 2 3 4 5 6 7
Blood Sugar Testing	On how many of the last SEVEN DAYS did you test your blood sugar?
	0 1 2 3 4 5 6 7
	On how many of the last SEVEN DAYS did you test your blood sugar the number of times recommended by your health care provider?
	0 1 2 3 4 5 6 7
Foot Care	On how many of the last SEVEN DAYS did you check your feet?
	0 1 2 3 4 5 6 7
	On how many of the last SEVEN DAYS did you inspect the inside of your shoes?
	0 1 2 3 4 5 6 7

- **FreeStyle Libre CGM**

FreeStyle Libre 14-day Flash Glucose Monitoring systems are CGM devices indicated for replacing blood glucose testing and detecting trends and tracking patterns aiding in the detection of episodes of hyperglycemia and hypoglycemia, facilitating both acute and long-term therapy adjustments in persons (age 18 and older) with diabetes. The systems are intended for single patient use and require a prescription.



Figure 3 FreeStyle Libre

This system provides real-time glucose results on scanning of interstitial fluid glucose, an 8-hour historical trends, and a trend arrow showing the direction the glucose is going. The users are advised to scan their sensors at least once in 8 hours to maintain their sensor active.

- **SEOUL Algorithm**

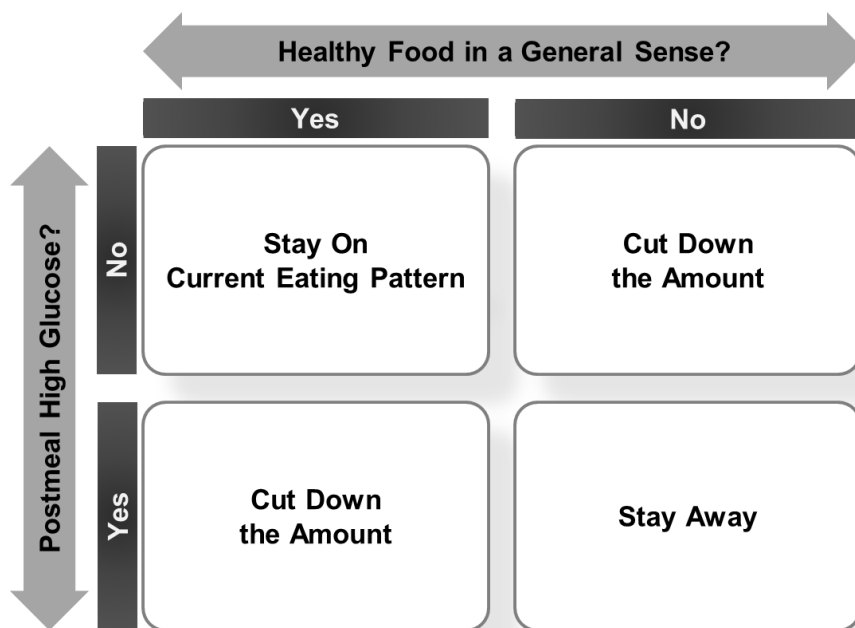


Figure 4 SEOUL Algorithm

SEOUL algorithm is a simple dietary advice in a 2×2 matrix that can be applied to enhance food consumption behavior based on individual postprandial glycemic response. Decisions will be made on individual basis according to the SEOUL algorithm. As glucose monitoring with CGM allows patients to evaluate their individual response to food, SEOUL algorithm will be a useful tool for guiding medical nutritional therapy with the scanned glucose values from CGM.

✓ **Healthy Food in a General Sense? O / Postmeal High Glucose? X**

This is good and healthy food for the person. The participant may continue eating a healthy meal with tolerable glycemic response after consuming the food.

✓ **Healthy Food in a General Sense? X / Postmeal High Glucose? X**

The participant should avoid an unhealthy meal that provokes postprandial hyperglycemia.

✓ **Healthy Food in a General Sense? O / Postmeal High Glucose? O**

If hyperglycemia is detected after consuming a meal that is generally considered to be healthy, reducing the amount of food is recommended. This may give health benefits to some people, but not the personalized diet of choice for the participant, especially if consumed in a large amount.

✓ **Healthy Food in a General Sense? X / Postmeal High Glucose? O**

Amount of unhealthy food should also be reduced even if it does not generate hyperglycemia upon ingestion. Even without postprandial hyperglycemia upon consuming the food, the food may have fewer nutritional values and may be high in fat or unhealthy ingredients.

● **PDF CGN Diary**

연속혈당측정결과 자가진단수첩

Patient-Driven lifestyle modification using
FreeStyle Libre in type 2 diabetes patients

연속혈당측정기를 지속적으로 착용하며 혈당변화를 스스로 관찰함으로써
내 몸이 딱 맞는 식습관과 운동습관을 형성할 수 있습니다.
측정 결과를 어떻게 활용할까요?

나에게 맞는 식습관

		일반적으로 건강에 좋다고 알려진 음식인가요?	
		예	아니오
이 음식 섭취 후 혈당이 많이 올라가요?	아니오	지금처럼 섭취하세요	섭취량을 조절하세요
	예	섭취량을 조절하세요	가급적 피하세요

예시를 살펴볼까요?

- “현미밥 + 야채계란찜 + **식교치킨장국**”을 먹었는데 혈당이 별로 안 올라갔어요.”
지금처럼 섭취하세요
- “짜장면 + 군만두를 먹었는데 혈당이 별로 안 올라갔어요.”
짜장면과 군만두는 칼로리가 높고 지방이 많은 음식입니다.
비록 혈당을 많이 올리지 않았더라도, 양을 조절하시는 것이 좋습니다.
- “비빔밥 + **깡이백식장국** + 고구마”를 먹었는데 혈당이 많이 올라갔어요.”
양을 많이 먹어서 혈당이 높아졌을 수 있습니다. 섭취량을 조절하세요
- “햄버거 + 감자튀김 + **콜라**”를 먹었는데 혈당이 많이 올라갔어요.”
가급적 피하세요

I. 오늘 하루 리브레로 혈당을 몇 번 확인하셨습니다? _____ 번

II. 식후 고혈당

아침 식후 고혈당이 있었나요?

① 네
② 아니오

식후 고혈당은 어떻게 대처하셨나요?

① 산책 등의 운동
② 다음 식사 때 식사량 조절
③ 기타 ()

점심 식후 고혈당이 있었나요?

① 네
② 아니오

식후 고혈당은 어떻게 대처하셨나요?

① 산책 등의 운동
② 다음 식사 때 식사량 조절
③ 기타 ()

저녁 식후 고혈당이 있었나요?

① 네
② 아니오

식후 고혈당은 어떻게 대처하셨나요?

① 산책 등의 운동
② 다음 식사 때 식사량 조절
③ 기타 ()

간식을 드셨나요? → 무엇을 드셨나요? → 간식을 먹은 후
① 네 ② 아니오

III. 특별히 혈당을 올리는 음식이 있었다면 무엇이었습니다? _____

IV. 혈당을 많이 올리지 않는 음식이 있었다면 무엇이었습니다? _____

V. 저혈당

저혈당이 있었나요?

① 네
② 아니오

저혈당은 왜 나타났을까요?

① 평소보다 적게 먹음
② 활동량(운동) 증가

VI. 운동

30분 이상 걸었습니까?

네 아니오

근력운동을 하셨습니까?

네 아니오

VII. 오늘 나의 혈당관리 점수는? _____ 점

😊

😊

😐

😞

😡

5
★★★★★

4
★★★★☆

3
★★★☆☆

2
★★☆☆☆

1
★☆☆☆☆

Figure 5 PDF CGM Diary

Each participant will receive a “PDF CGM Diary” that is composed of seven questions to answer and recollect the behavior for the day. The questions in the diary are as follows:

1. How many times did you scan your glucose with the FreeStyle CGM?
2. Postprandial hyperglycemia
 - A. Did you have hyperglycemia after breakfast?
 - i. If so, what caused hyperglycemia? (Multiple choices)
 - ii. What action did you take to resolve your hyperglycemia?
 - B. Did you have hyperglycemia after lunch?
 - i. If so, what caused hyperglycemia?
 - ii. What action did you take to resolve your hyperglycemia?
 - C. Did you have hyperglycemia after supper?
 - i. If so, what caused hyperglycemia?
 - ii. What action did you take to resolve your hyperglycemia?
 - D. Did you take snack? If so, what? Glucose level after snack?
3. Which food caused higher glucose than expected?
4. Which food did not increase your glucose levels as expected?
5. Hypoglycemia
 - A. Did you have hypoglycemia today?
 - B. If so, what caused hypoglycemia?

6. Exercise

A. Did you walk (or equivalent physical activities) for 30 minutes or more?

B. Did you do any resistance exercise?

7. Self-evaluation for the day (Scores: 1–5)

- **BGM Devices**

Each participant in the control group will be assigned a glucose meter to record their blood glucose values during the study. Participants will be recommended to monitor their glucose at least once or twice daily during the study period.



Figure 6 Blood glucose meter

As an ancillary device, participants in the control group will also be provided with a glucose logbook to keep track of their everyday premeal/postmeal and before bedtime glucose. This logbook is self-created by the PDF study team, but the structure and design are alike customary logbooks.

나의 혈당 수첩

대상자 번호: R _____
제공 날짜: 20__년__월__일

날짜	아침		점심		저녁		취침 전	혈압	비고
	식전	식후	식전	식후	식전	식후			
월	일								
월	일								
월	일								
월	일								
월	일								
월	일								
월	일								

Figure 7 Glucose logbook

IX. Data Collection and Management

Data collected during the study will be documented on electric case report forms (CRFs). Guarantors will have full access to all the data in the study and takes responsibility for the integrity of the of the data and the accuracy of the data analysis.

X. Statistical Considerations

The approach to sample size calculation and outcome measures have been described in detail

in the previous section. For all primary and secondary outcomes, site of recruitment will be adjusted as random effects and the baseline measures as covariates.

Primary analysis will be conducted with the modified intention-to-treat (mITT) approach.

Per protocol (PP) analysis will be conducted as an adjunctive. It is defined as a subset of the ITT population who completed the study without any major protocol violations. PP analyses exclude all protocol violators, including anyone who did not adhere to treatment, switched groups, or missed measurements.

Analysis	Group	Definition
mITT	Intervention	<ul style="list-style-type: none"> ✓ Participants will be eligible for analysis if visits are made within 12 weeks from the entry visit and more than one laboratory values including HbA1c are conducted ✓ Participants will be eligible for analysis if the subjects had had at least 14 days of CGM wear and one or more ambulatory glucose profile reports are available at LibreView site
	Control	<ul style="list-style-type: none"> ✓ Participants will be eligible for analysis if visits are made within 12 weeks from the entry visit and more than one laboratory values including HbA1c are conducted
PP	Intervention	<ul style="list-style-type: none"> ✓ Participants will be eligible for analysis if visits are made at 12 weeks from the entry visit and all laboratory values including HbA1c are fully conducted ✓ 5 or more of the provided CGM devices have been used ✓ Average data capture rate of 80% or more (percent active time on CGM) ✓ At least 80% completion of the PDF CGM Diary
	Control	<ul style="list-style-type: none"> ✓ Participants will be eligible for analysis if visits are made at 12 weeks from the entry visit and all laboratory values including HbA1c are fully conducted

All analyses will be performed using IBM SPSS Statistics version 27.0 (IBM Corp., Armonk, NY, USA) and R version 4.1.2 (The R Foundation for Statistical Computing, Vienna, Austria, <http://www.R-project.org>). A two-sided *P* value of less than 0.05 will be considered statistically significant.

XI. Adverse Events

The severity of any adverse events will be rated as mild/moderate/severe. However, anticipated study or device-related adverse events are expected to be none or mild.

- **Anticipated Adverse Effects**

- ✓ For any detected hyperglycemia of 270 mg/dL or higher for three consecutive days during the first 6 weeks of the study, participants will be advised to report to the clinical center of recruitment site.
- ✓ For any detected hyperglycemia of 240 mg/dL or higher for three consecutive days during the second 6 weeks of the study, participants will be advised to report to the clinical center of recruitment site.
- ✓ Rescue therapy may be considered for severe hyperglycemia.
- ✓ For any detected hypoglycemia of lower than 70 mg/dL, participants will be advised to report to the clinical center of recruitment site to assess for severity and additional visits to the center will be made if necessary.
- ✓ For severe hypoglycemia, adjustment of the diabetes medication would be considered and for those who were previously not on any hypoglycemic agents, comprehensive evaluation of the disease status will be conducted.
- ✓ Glucose levels of higher than 180 mg/dL, 250 mg/dL will be documented as level 1, level 2 hyperglycemia, respectively.
- ✓ Glucose levels of less than 70 mg/dL, 54 mg/dL will be documented as level 1, level 2 hypoglycemia, respectively.
- ✓ Insertion of CGM sensors into the skin may cause mild pain, erythema, and/or edema

at the insertion site. Infection, excessive bleeding, or hematoma are also possible complications of device use. Participants may experience irritation or allergic reactions on the site of sensor insertion, which will be similar to allergies that may occur with contact with medical tape. Most of these adverse events are expected to be mild, reversible, and infrequent.

- **Unanticipated Adverse Effects**

Any adverse effects will be reported to the center, and the investigator will categorize the relationship of the event to the study.

Table 1 Schedule of Study Events

Time item	Monthly Schedule																							
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22	23	24
Enroll																								
V1																								
V2																								
Phone/ remote contact																								
Confirm study closure																								
Analysis																								
Review																								

XII. References

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