nature medicine

Supplementary information

https://doi.org/10.1038/s41591-025-03823-3

DASH4D diet for glycemic control and glucose variability in type 2 diabetes: a randomized crossover trial

In the format provided by the authors and unedited

Supplemental Table 1: Effects of the DASH4D (versus comparison) diet on primary outcomes - sensitivity analyses

	Comparison diet	DASH4D diet	Adjusted mean difference (95% CI)	P-value
Sensitivity analysis #1 – Per protocol – Only includes participants with >90% dietary adherence (N=85)				
Mean sensor glucose, mg/dL	142.0 (135.2, 148.8)	131.3 (124.2, 138.3)	-10.8 (-15.5, -6.0)	<0.001
Mean time-in-range, %	78.5 (74.6, 82.4)	83.6 (79.5, 87.6)	5.1 (2.5, 7.6)	<0.001
Mean coefficient of variation, %	26.1 (24.9, 27.4)	26.0 (24.7, 27.3)	-0.2 (-1.2, 0.9)	0.74
Sensitivity analysis #2 – Only includes CGM assessments based on ≥10 days of wear time (N=85)				
Mean sensor glucose, mg/dL	142.5 (134.6, 150.3)	132.3 (124.4, 140.1)	-10.2 (-15.1, -5.2)	<0.001
Mean time-in-range, %	78.3 (74.1, 82.4)	83.4 (79.2, 87.5)	5.1 (2.5, 7.7)	<0.001
Mean coefficient of variation, %	26.1 (24.9, 27.4)	25.5 (24.3, 26.8)	-0.6 (-1.3, 0.2)	0.12

Abbreviations: CI = confidence interval

Note: Time-in-range was defined as the percentage of time spent with CGM glucose between 70 and 180 mg/dL. Estimates are means (with 95% CIs) calculated using linear mixed-effects models. Each model included a random intercept for participants and adjusted for study feeding period. Outcomes were based on up to 14 days of CGM data, typically measured starting during week 3 of each feeding period.

Supplemental Table 2: Effect of the DASH4D (versus comparison) diet on post-hoc outcomes (N=89)

	Comparison diet	DASH4D diet	Adjusted mean difference (95% CI)
Glucose Management Indicator, %	6.7 (6.6, 6.9)	6.5 (6.3, 6.7)	-0.3 (-0.4, -0.2)
Glycemia Risk Index	0.4 (0.3, 0.5)	0.3 (0.2, 0.4)	-0.1 (-0.2, -0.0)

Abbreviations: CGM = continuous glucose monitoring; CI = confidence interval

Note: Estimates are means (with 95% CIs) calculated using linear mixed-effects models. Each model included a random intercept for participants and adjusted for study feeding period. Outcomes were based on up to 14 days of CGM data, typically measured starting during week 3 of each feeding period.

Supplemental Table 3: Power calculations for the DASH-CGM ancillary study

The sample size for DASH4D-CGM study was fixed per the design of the parent DASH4D Trial. Assuming a sample size of 100 participants, the parent trial was designed to detect a 4.7 mmHg difference in systolic blood pressure between the DASH4D diet with lower sodium and the comparison diet with higher sodium with 90 % power (2-sided test with $\alpha = 0.05$). In the DASH4D-CGM ancillary study, we assumed that dietary sodium would not impact glucose levels. Therefore, we prespecified combining the two sodium arms of CGM data to maximize statistical power.

We used data from the Hyperglycemic Profiles in Obstructive Sleep Apnea (HYPNOS) trial to estimate the within-person correlation and variance for different CGM metrics. Participants in HYPNOS wore the Abbott Libre Pro at two different time points (baseline and at the 3-month follow-up visit). Each CGM assessment lasted up to 14 days. This is the same CGM device that was used for CGM assessment in the DASH4D-CGM study. The study population for HYPNOS population (184 adults with type 2 diabetes not treated with insulin from the Baltimore area) was also similar to the population enrolled in the DASH4D study.

We calculated the minimal detectable differences for the primary outcomes (mean glucose, time-in-range, and coefficient of variation) for three scenarios: parallel design with 2 weeks of CGM in each diet; crossover design with 2 weeks of CGM in each diet; and crossover design with 4 weeks of CGM (two sodium arms combined) in each diet.

The within-person correlation of the primary outcomes ranged from 0.69 (mean glucose) to 0.77 (coefficient of variation). The standard deviation of the metrics using the crossover design was substantially lower than a parallel design. Combining the CGM for higher and lower sodium periods reduced the variance by 50%.

The final three columns show that minimal detectable difference for the primary outcomes. The crossover design of the DASH4D trial has approximately twice the power as compared to a parallel design (11.8 vs. 20.3 mg/dL for mean glucose, 5.9 vs. 11.0 % for time-in-range, and 1.4 vs. 3.0 % for coefficient of variation). Combining the two sodium arms in the crossover design further improved our ability to detect small effect sizes (8.8 mg/dL for mean glucose, 4.2 % for time-in-range, and 1.0 % for coefficient of variation).

					Standard Deviation of Change		Variance ratio cross-over vs. parallel arm design		Sample size ratio 4 diets/person vs. parallel 1		Minimal detectable difference at 90% power (assuming N = 100)		
	Feeding Period 1 Mean (SD)	**Feeding Period 2 Mean (SD)**	**P2 – P1 Mean (SD)**	**Correlation (*r*) P1 to P2**	**Crossover design (1)**	**Parallel design (2)**	**One period (3)**	**Two periods combined (4)**	**One period (5)**	**Two periods combined (6)**	**Parallel design (7)**	**Crossover, one period (8)**	**Crossover, two periods combined (9)**
Mean glucose, mg/dL	149.5 (39.1)	159.2 (49.1)	9.7 (36.3)	0.69	36.3	62.6	0.34	0.17	36	142	20.3	11.76	8.83
TIR, %	74.1 (22.0)	68.5 (26.0)	-5.8 (18.3)	0.72	18.3	34	0.29	0.14	48	192	11	5.93	4.19
CV, %	0.27 (0.06)	0.27 (0.07)	-0.006 (0.044)	0.77	0.044	0.091	0.23	0.12	74	296	3	0.014	0.01

Abbreviations: P1=Period 1; P2=Period 2; TIR, % time in range 70-180 mg/dL; CV, coefficient of variation.

Columns definitions: (1) SD of P2-P1; (2) Square root of the sum of P1 and P2 variances; (3) Square of the ratio of the SD in previous two columns; (4) Cross-over variance is reduced by 50% due to combining two CGMs (lower and higher sodium feeding periods) for each DASH or typical diet; (5) Four divided by the variance ratio in column (3) (parallel arm design requires 4 people for 4 diets vs. 1 person fed 4 diets in DASH4D); (6) Four divided by the variance ratio in column (4); (7-9) calculated using 2-tailed alpha=0.05 with N=100.

CONSORT 2010 checklist of information to include when reporting a randomised trial*

Section/Topic	Item No	Checklist item	Reported on page No
Title and abstract			
	1a	Identification as a randomised trial in the title	1
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts)	1
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale	3
	2b	Specific objectives or hypotheses	3
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio	25
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons	NA
Participants	4a	Eligibility criteria for participants	25-28
	4b	Settings and locations where the data were collected	25
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	28-29
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed	30-32
	6b	Any changes to trial outcomes after the trial commenced, with reasons	NA
Sample size	7a	How sample size was determined	31-32
	7b	When applicable, explanation of any interim analyses and stopping guidelines	NA
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	29-30
	8b	Type of randomisation; details of any restriction (such as blocking and block size)	29-30
Allocation concealment mechanism	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	29-30
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	29-30
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those	29-30

		assessing outcomes) and how	
	11b	If relevant, description of the similarity of interventions	28-29
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes	32
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	32
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analysed for the primary outcome	Figure 1
	13b	For each group, losses and exclusions after randomisation, together with reasons	Figure 1
Recruitment	14a	Dates defining the periods of recruitment and follow-up	4
	14b	Why the trial ended or was stopped	NA
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	Table 1
Numbers analysed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups	Table 2
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	Table 2, Fig 2
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	Table 2
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	Fig 4
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	6
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses	9
Generalisability	21	Generalisability (external validity, applicability) of the trial findings	9
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	6-9
Other information			
Registration	23	Registration number and name of trial registry	2
Protocol	24	Where the full trial protocol can be accessed, if available	Attached with submission
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	10

Citation: Schulz KF, Altman DG, Moher D, for the CONSORT Group. CONSORT 2010 Statement: updated guidelines for reporting parallel group randomised trials. BMC Medicine. 2010;8:18.

*We strongly recommend reading this statement in conjunction with the CONSORT 2010 Explanation and Elaboration for important clarifications on all the items. If relevant, we also recommend reading CONSORT extensions for cluster randomised trials, non-inferiority and equivalence trials, non-pharmacological treatments, herbal interventions, and pragmatic trials. Additional extensions are forthcoming: for those and for up-to-date references relevant to this checklist, see www.consort-statement.org.

Effects of the DASH diet on glucose patterns in adults with type 2 diabetes

The Dietary Approaches to Stop Hypertension for Diabetes (DASH4D) Trial Continuous Glucose Monitoring (CGM) Ancillary Study

Extracted from Appendix B of the DASH4D

PROTOCOL

and

STATISTICAL ANALYSIS PLAN (SAP)

Version 2.6
November 1, 2024

Protocol Number: IRB00232059
ClinicalTrials.gov Number: NCT04286555

Principal Investigator: Elizabeth Selvin, PhD, MPH,
Johns Hopkins Bloomberg School of Public Health

Funded by: The National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), Grant # R01DK128900

Ancillary Study Integration into the Main Trial

The DASH4D-CGM Study is an ancillary study embedded in the main trial (DASH4D Trial). The DASH4D-CGM ancillary study was approved as part of the same institutional review board (IRB) application as an appendix to the main protocol. CGM procedures, risks, and benefits were included as part of the consent form that participants signed for the main trial. The ancillary study is part of the ClinicalTrials.gov registration for the main trial. Identifying information for the DASH4D-CGM ancillary study appear on the cover page of this protocol, and administrative details of the main trial are provided here. The subsequent sections reflect the DASH4D-CGM ancillary study appendix to the main protocol.

Main Trial Title:	Dietary Approaches to Stop Hypertension for Diabetes (DASH4D) Trial
Main Trial PIs:	Lawrence J. Appel, MD, MPH, Scott J. Pilla, MD, MHS, and Hsin-Chieh Yeh, PhD Johns Hopkins University School of Medicine
Main Trial Funded By:	Sheikh Khalifa Stroke Institute at Johns Hopkins University

Table of Contents

History of Protocol Changes

The following table summarizes substantive changes between protocol versions. Minor changes, such as minor corrections and clarifications, page numbering, and formatting are not described in the table but can be seen in the track changes versions of the protocol.

Protocol version	Affected section(s)	Brief description of change	Brief rationale for change
v2.0 (03-21-2021)	Version of the protocol approved and in use at the time of enrollment of the 1st DASH4D participant.		
v2.1 (09-29-2021)	6.2 Eligibility Criteria; Appendix E 21.4 Exclusions	For the CGM ancillary, implantable pacemaker was added as an exclusion criterion.	The CGM sensor's manufacturer has not extensively tested the use of the sensor in conjunction with use of an implantable pacemaker, so this exclusion was added out of an abundance of caution.
	8.1 Data Collection Schedule – Table 3; Appendix E 21.6 Symptom Reporting Survey	Addition of a symptom reporting survey during each period of CGM sensor wear.	Reporting of symptoms will allow investigators to learn more about the relationship between changes in glucose levels and symptoms experienced.
v2.3 (11-01-2023)	Appendices	Appendices A-D were consolidated into a single Appendix A; former Appendix E was relabeled Appendix B and its sections were renumbered; former Appendix F was deleted; and a new Appendix C was added.	Updates to the Appendices were made to better represent these materials as separate from but attached to the protocol.
v2.4 (02-28-2024)	Appendix B, 1. Ancillary Study Details	New section added with details of the ancillary study.	Although fully embedded in the DASH4D data collection protocol and consistent with the main study's outcomes and objectives, this CGM ancillary study was funded by a separate grant, and those details have been added.
	Appendix B, 2. Rationale	Added a sentence to indicate that the ancillary study also includes examination of biomarkers.	Examination of biomarkers was included in the funded CGM ancillary study.
v2.5 (07-26-2024)	Appendix B	Clarified the timing of the CGM placement and data collection.	Clarified that the CGM sensors are typically placed during the last day of in-person feeding during week 3 and worn for up to 14 days.
	Appendix B, 10. Study Outcomes and Objectives	Section added.	Details on the CGM ancillary study's outcomes and objectives have been added. This information was added prior to the CGM team being unblinded to randomized diet sequence.

Protocol version	Affected section(s)	Brief description of change	Brief rationale for change
v2.5 (07-26-2024)	Appendix B, 11. Statistical Analysis	Section added.	Details on the CGM ancillary study's analysis plans have been added. This information was added prior to the CGM team being unblinded to randomized diet sequence.
v2.6 (11-01-2024)	Appendix B, 10. Study Outcomes and Objectives; Appendix B, 11. Statistical Analysis	Updated to reflect that the CGM ancillary study will compare the DASH4D diet to the comparison diet, combining across the sodium levels, rather than focusing on the contrast between the DASH4D diet with lower sodium and the comparison diet with higher sodium.	The CGM ancillary study hypothesized that sodium would not have an effect on glucose, and the grant proposal had indicated that data would be combined across the DASH4D diet with lower sodium and DASH4D diet with higher sodium, and likewise combined for the comparison diet with lower sodium and comparison diet with higher sodium, to increase statistical power. The previous version of the CGM statistical analysis plan had been modeled off of the main trial's SAP inadvertently and is now being updated to match the original planned analytic approach for the ancillary study.
	Appendix B, 10. Study Outcomes and Objectives	The time in range, time above range, and time below range outcomes were more clearly defined for the specific ranges and separated into a few different ranges of interest.	There are multiple glucose ranges of interest for the CGM ancillary study, and the outcomes were updated to more clearly reflect these ranges.
	Appendix B, 10. Study Outcomes and Objectives	Exploratory CGM outcomes were added.	These planned exploratory outcomes were not specified in the previous version of the CGM SAP.
	Appendix B, 11. Statistical Analysis	Exploratory analyses were added.	The planned exploratory analyses were not specified in the previous version of the CGM SAP.

Continuous Glucose Monitoring (CGM) Ancillary Study

1. Ancillary Study Details

Official Project Title: Effects of the DASH diet on glucose patterns in adults with type 2 diabetes

Principal Investigator: Elizabeth Selvin, PhD, MPH
Johns Hopkins Bloomberg School of Public Health

Funded By: National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK)

Grant #: R01DK128900

2. Rationale

The overarching goal is to evaluate how the DASH4D dietary pattern modifies glucose patterns in adults with type 2 diabetes. This ancillary study to the DASH4D protocol will add continuous glucose monitoring (CGM) combined with symptom reporting in all participants in the DASH4D trial (N=~100) during screening (between SV2 and the start of the run-in) and during the two weeks at the end of each of four feeding periods. This ancillary study also includes laboratory testing for diabetes and cardiac biomarkers of biospecimens collected as part of the main DASH4D trial. This study will answer the question: Does the DASH4D diet (a DASH-style diet modified for people with diabetes) improve glucose control and reduce glycemic variability in adults with type 2 diabetes?

3. Background

Dietary guidelines for persons with diabetes are largely directed at reducing hyperglycemia. The DASH diet[1] is rich in fruits, vegetables, and low-fat dairy products with reduced saturated fat and cholesterol. The DASH eating plan is recommended by the ADA for adults with diabetes based on evidence that it helps control blood pressure and lowers cardiovascular risk in the general population.[2,3] The direct effects of the DASH diet on glucose control and glycemic excursions are uncharacterized. The DASH4D trial provides an opportunity to evaluate how diet may affect hyperglycemia and glucose patterns using CGM. Glucose patterns in adults with type 2 diabetes are relatively uncharacterized, and no prior study has examined the effect of diet on CGM parameters in a controlled feeding study. The addition of the symptom reporting survey during CGM wear will allow us to understand how certain symptoms relate to changes in glucose levels.

4. Study design

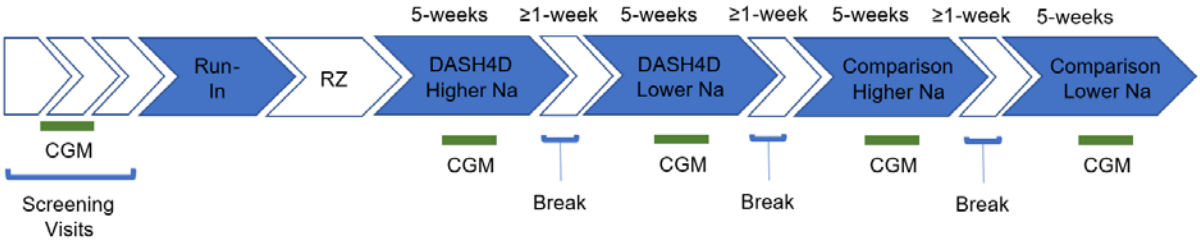
We propose to add 14-day CGM assessment in participants in the DASH4D trial (N=~100) during screening (up to 14 days, or the start of Run-In, whichever comes first) and each of the four feeding periods, for a total of five 14-day CGM periods (see green lines in **Figure CGM-1**).

As part of the main trial, each participant will complete screening, a run-in period, and four feeding periods lasting 5 weeks each, separated by at least 1 week of a break (eating own food).

During the screening phase and at randomization, DASH4D screenees will be invited to participate in, and consent for, this ancillary study, which is optional. CGM sensors will be placed during week 3 of each feeding period (typically on Thursday, which is the last day of in-person feeding every week). Sensors will be worn up to 14 days. Thus, CGM data collection will typically begin during week 3 and end during week 5 for every feeding period.

During each period of CGM device wear, we will also ask participants to complete a symptom reporting survey at least daily to indicate whether they experienced any symptoms that may relate to changes in their glucose levels, along with reporting the time of symptom onset.

Figure CGM-1. Design of the DASH4D CGM Study.



Abbreviation: RZ = randomization
Note: Figure shows an example of randomization to 1 of 24 possible orders of diet administration.
Total of 7-9 months per participant including 20 (=4 periods * 5) weeks of controlled diet

5. Exclusions

Participants will be excluded from participating in the CGM ancillary study if they have a history of allergic skin reaction to adhesive or an implantable medical device, such as a pacemaker. Participants who do not wish to participate in the CGM ancillary study will still be allowed to participate in the DASH4D trial.

6. Procedures

We will use the FreeStyle Libre Pro CGM device (Abbott; https://provider.myfreestyle.com/freestyle-libre-pro-product.html) to measure glucose in up to five 14-day periods (during screening, CGM wear may be <14 days) in all participants who consent to this protocol (**Figure CGM-2**). The version of the device used in this ancillary study does not reveal the glucose readings to participants, which will be provided to participants after the data collection phase of the trial ends (see section 9 Reporting below).

Figure CGM-2. FreeStyle Libre Pro CGM System.

The FreeStyle Libre Pro system is FDA approved for use in continuous monitoring of glucose in persons with diabetes who are aged 18 or older. The system is designed for professional use to reveal glucose trends and patterns, which are downloaded from the sensor using a reader following up to 14 days of wear. The sensor is held in place with an adhesive and has two main parts: 1) a transmitter patch, which is about the diameter of a quarter and thickness of two quarters that collects and stores data on glucose, and 2) a flexible very thin filament (<4mm) sensor inserted just under the skin to measure interstitial glucose. The application of the sensor is painless and most patients report that they cannot feel the sensor when it is being worn.

After obtaining informed consent as part of the main screening and trial consents, trained study staff will place the sensor on the back of the upper arm using a disposable applicator at SV1 and during the third week of each of the four feeding periods. The sensor will be covered with an adhesive bandage designed for use with the Libre sensor to prevent accidental dislodgement. At least 2 minutes after placement, staff will check the status of each sensor to ensure it is working properly.

The sensor is worn on the arm for 14 days (may be shorter during screening) and is factory calibrated (no fingerstick is required). The Libre Pro system records interstitial glucose every 15 minutes and stores the 14 days of data. DASH4D participants will be provided with instructions for wear of the device. The device stays on for each 14-day period and can be worn while showering, swimming, or exercising. Staff will be available (in-person and by phone) to answer any questions and will encourage participants to wear the device for the full 14-day period. After day 14 of each wear period, staff will remove the device during the next pre-scheduled trial visits. The Libre Pro sensors require a hand-held reader to download information on glucose values. After removal, sensors will be labeled, and the data will be downloaded by staff using the Libre Pro Reader (**Figure CGM-3**).

Figure CGM-3. Libre Pro Reader.

7. Symptom Reporting Survey

During each period of CGM device wear, participants will be asked to complete a symptom reporting survey to report each time they experience one of the listed symptoms, along with the time of symptom onset, or to report that none of the symptoms of interest occurred that day. Participants will ideally complete the symptom reporting via REDCap survey links that will be sent via text message, so that they can better report symptoms in real-time or near real-time. However, participants may elect to complete the symptom reporting as a paper-based diary if they do not wish to receive text messages or complete a mobile survey.

8. Safety/Risks

There is minimal risk or discomfort associated with use of the CGM sensor. The main risk is skin irritation from the adhesive. There is a very small risk of developing a local skin infection at the site of the sensor filament placement. The risk will be mitigated by using sterile technique during placement. The Libre Pro system does not have alarms and does not provide any real-time information to the participant. Throughout the trial, participants will continue routine glucose monitoring as recommended by their doctor. Participants will be counseled not to ignore symptoms that may be due to low or high blood glucose, or dehydration. The CGM device is contraindicated for wear during MRI, CT scan, X-ray, or diathermy treatment. During any medical treatment, participants should inform their health care provider that they are wearing a CGM sensor. The sensor should be removed before any MRI, CT scan, X-ray, or diathermy treatment. Confidentiality will be maintained by labeling the used sensors with a coded number and following data security procedures already in place as part of the DASH4D trial.

9. Reporting

Participants will not be aware of their glucose measures collected during the 14-day wear periods. A report with a summary of the 14-day glucose data from the screening phase (mean glucose, standard deviation, and a graph of glucose values with information on the normal range)

will be provided back to participants after they complete the feeding phase of the trial or are closed out of screening (i.e., not randomized). CGM technology is often used in the care of adults with type 1 diabetes. It is not standard of care for adults with type 2 diabetes, and it is not commonly used in this population. Even if subsequent analysis of the CGM data reveals clinically relevant glucose patterns, this information is not directly clinically actionable at a later date, especially in the absence of insulin therapy.

10.Study Outcomes and Objectives

Based on prior studies, we hypothesized that salt would have no effect on glucose.[4] Therefore, we plan to combine data from the lower and higher sodium feeding periods for each diet to increase statistical power (i.e., combine data collected during the DASH4D lower sodium diet with data collected during the DASH4D higher sodium diet). Our primary aim is to examine the effects of the DASH4D diet (vs. comparison diet) on glucose control and glycemic variability in adults with type 2 diabetes.

Primary, secondary, and exploratory CGM outcomes were selected based on clinical guidelines and recommendations from a consensus statement on CGM endpoints for clinical trials.[5,6] CGM outcomes will be based on CGM data captured by sensors worn from week 3 to week 5 (up to 14 days) of each 5-week feeding period in participants included in the DASH4D-CGM ancillary study. Per current analytic recommendations,[6] CGM outcomes will be generated using all available CGM data for each feeding period.

10.1 Primary CGM outcomes

10.1.1 **CGM mean glucose (mg/dl):** The mean of glucose measurements collected during the 14-day wear period will be used as a primary outcome of the corresponding feeding period.

10.1.2 **Percentage of time between 70 and 180 mg/dL:** The percentage of time glucose was between 70 and 180 mg/dL (time-in-range) during the 14-day wear period will be used as a primary outcome of the corresponding feeding period.

10.1.3 **Coefficient of variation (%):** The coefficient of variation (standard deviation divided by mean glucose, multiplied by 100) of glucose measurements collected during the 14-day wear period will be used as a primary outcome of the corresponding feeding period.

10.2 Secondary CGM outcomes

10.2.1 **Glucose standard deviation (mg/dL):** The standard deviation of glucose measurements will be used as a secondary outcome of the corresponding feeding period.

10.2.2 **Percentage of time above 180 mg/dL:** The percentage of time glucose was above 180 mg/dL will be used as a secondary outcome of the corresponding feeding period.

10.2.3 **Percentage of time above 250 mg/dL:** The percentage of time glucose was above 250 mg/dL will be used as a secondary outcome of the corresponding feeding period.

10.2.4 **Percentage of time below 70 mg/dL:** The percentage of time glucose was below 70 mg/dL will be used as a secondary outcome of the corresponding feeding period.

10.2.5 **Percentage of time below 54 mg/dL:** The percentage of time glucose was below 54 mg/dL will be used as a secondary outcome of the corresponding feeding period.

10.3 Exploratory CGM outcomes

10.3.1 **Percentage of time between 70 and 140 mg/dL:** The percentage of time glucose was between 70 and 140 mg/dL will be used as an exploratory outcome of the corresponding feeding period.

10.3.2 **Percentage of time above140 mg/dL:** The percentage of time glucose was above 140 mg/dL will be used as an exploratory outcome of the corresponding feeding period.

10.3.3 **Proportion of participants with >70% time between 70 to 180 mg/dL:** The proportion of participants that spent >70% of time with glucose between 70 and 180 mg/dL will be used as an exploratory outcome of the corresponding feeding period.

10.3.4 **Proportion of participants with coefficient of variation <36%:** The proportion of participants with coefficient of variation <36% will be used as an exploratory outcome of the corresponding feeding period.

10.3.5 **Proportion of participants with <25% time above 180 mg/dL:** The proportion of participants that spent <25% of time with glucose above 180 mg/dL will be used as an exploratory outcome of the corresponding feeding period.

10.3.6 **Proportion of participants with <5% time above 250 mg/dL:** The proportion of participants that spent <5% of time with glucose above 250 mg/dL will be used as an exploratory outcome of the corresponding feeding period.

10.3.7 **Proportion of participants with <4% time below 70 mg/dL:** The proportion of participants that spent <4% of time with glucose below 70 mg/dL will be used as an exploratory outcome of the corresponding feeding period.

10.3.8 **Proportion of participants with <1% time below 54 mg/dL:** The proportion of participants that spent <1% of time with glucose below 54 mg/dL will be used as an exploratory outcome of the corresponding feeding period.

10.4 Primary aim

Examine the mean differences in mean glucose, time-in-range, and glucose coefficient of variation on the DASH4D diet compared to the comparison diet, in a combined analysis across both levels of sodium.

- We hypothesize that the DASH4D diet will result in improved glucose control (lower mean glucose, higher time-in-range) and glycemic variability (lower glucose coefficient of variation) compared to the comparison diet.

10.5 Secondary aims

10.5.1 Examine the mean differences in glucose standard deviation and time spent with hyperglycemia and hypoglycemia on the DASH4D diet compared to the comparison diet, in combined analyses across both levels of sodium.

10.5.2 Examine the mean differences in exploratory outcomes (described in 10.3) on the DASH4D diet compared to the comparison diet, in combined analyses across both levels of sodium.

11. Statistical Analysis

11.1 Analytic population

Among all randomized participants, those who completed CGM during one or more feeding period will be included in the analyses.

11.2 Statistical analyses

All primary analyses are summarized in **Table CGM-1**. We will conduct all primary analyses using an intention-to-treat approach. We will use linear (for continuous outcomes) or logistic (for binary outcomes) mixed effect models and compare differences in CGM outcomes while consuming the DASH4D (versus comparison) diet.

Our primary contrast will be between the DASH4D and comparison diet (combining across both levels of sodium) on mean glucose, time-in-range, and coefficient of variation (**Primary Aim – 10.4**). Secondary contrasts will assess the effects of the DASH4D (versus comparison) diet on glucose standard deviation, time spent with hyperglycemia, and time spent with hypoglycemia (**Secondary Aim – 10.5.1**) and on exploratory outcomes (**Secondary Aim – 10.5.2**). Because CGM outcomes are not independent, we will not make adjustments for multiple comparisons.

We will conduct several sensitivity analyses. First, to test our assumption that sodium does not affect glucose, we will assess the effects of the higher (versus lower) sodium diet on all primary CGM outcomes, stratified by different diets (**Sensitivity analysis 1a**). We will also examine whether the effects of the DASH4D diet on all CGM outcomes are modified by sodium levels by exploring diet-sodium interactions (**Sensitivity analysis 1b**). Second, we will re-estimate all analyses using a per-protocol approach **(Sensitivity analysis 2)**. For these analyses, participants without perfect adherence on >90% of days for a given diet will be excluded. Perfect adherence

was defined as eating all provided study foods and not eating any non-allowed foods or beverages.
For each feeding period, we will only include data from participants who wore CGM sensors for 10 or more days (**Sensitivity analysis 3**). Current guidelines suggest that sensors may need to be worn ≥70% of the time (~10 out of 14 days for the Abbott Libre Pro) to accurately represent glycemic control.[6]

11.3 Exploratory analyses

We will conduct two sets of exploratory analyses. First, we will estimate the linear mixed models to examine the effect the DASH4D (versus comparison) diet on the main CGM outcomes, stratified by age (<65, 65+), sex (male, female), baseline HbA1c (<7%, 7-7.9%, 8-8.9%), number of glucose-lowering medications used (0, 1, 2+), and type of diabetes medications used (no medication used, non-insulin or sulfonylureas, insulin or sulfonylurea). The DASH4D-CGM study is not powered to detect differences across any specific subgroup. Therefore, these analyses are exploratory and will not be adjusted for multiple comparisons.

Second, we will visually compare average hourly and daily mean glucose, time-in-range, and coefficient of variation across the DASH4D (versus comparison) diet. These analyses are exploratory and designed to examine how long participants may need to consume the DASH4D diet before an effect is evident and whether diet effects vary across daytime versus nighttime. Daily averages will be calculated using each 24-hour of CGM data. These analyses are similar to results reported in other major CGM trials.[7-10]

Table CGM-1: Summary of main comparisons for the CGM ancillary study

Aim	Outcomes	Contrast	Timing
Primary - 10.4	Mean glucose, TIR, CV	DASH4D vs Comparison	FP week 3-5
Secondary - 10.5.1	SD, TA180, TA250, TB70, TB54	DASH4D vs Comparison	FP week 3-5
Secondary - 10.5.2	See 10.3 for full list	DASH4D vs Comparison	FP week 3-5
Sensitivity analysis 1a	Mean glucose, TIR, CV	DH vs DL; CH vs CL	FP week 3-5
Sensitivity analyses 1b	Mean glucose, TIR, CV	(DH-DL) vs (CH-CL)*	FP week 3-5
Sensitivity analysis 2	Mean glucose, TIR, CV	DASH4D vs Comparison (Per-protocol)	FP week 3-5
Sensitivity analysis 3	Mean glucose, TIR, CV	DASH4D vs Comparison (CGM wear time >70%)	FP week 3-5

Note: All analyses will be conducted using an intention-to-treat approach unless otherwise stated.

Abbreviations: TIR = time-in-range; CV = coefficient of variation; SD = standard deviation; TA180 = time above 180 mg/dL; TA250 = time above 250 mg/dL; TB70 = time below 70 mg/dL; TB54 = time below 54 mg/dL; CH = Comparison diet with higher sodium; CL = Comparison diet with lower sodium; DH = DASH4D diet with higher sodium; DL = DASH4D diet with lower sodium; FP = feeding period

*Examination of interaction (difference of differences)

References

1. Appel LJ, Moore TJ, Obarzanek E, et al. A clinical trial of the effects of dietary patterns on blood pressure. DASH Collaborative Research Group. *N Engl J Med.* 1997;336(16):1117-1124.
2. American Diabetes Association. 5. Facilitating Positive Health Behaviors and Well-being to Improve Health Outcomes: Standards of Care in Diabetes-2024. *Diabetes Care.* 2024;47(Suppl 1):S77-s110. PMCID: PMC10725816
3. American Diabetes Association. 5. Lifestyle Management: Standards of Medical Care in Diabetes-2019. *Diabetes Care.* 2019;42(Suppl 1):S46-s60.
4. Patel SM, Cobb P, Saydah S, Zhang X, de Jesus JM, Cogswell ME. Dietary sodium reduction does not affect circulating glucose concentrations in fasting children or adults: findings from a systematic review and meta-analysis. *The Journal of nutrition.* 2015;145(3):505-513.
5. American Diabetes Association. 6. Glycemic goals and hypoglycemia: Standards of Care in Diabetes—2024. *Diabetes Care.* 2024;47(Supplement_1):S111-S125.
6. Battelino T, Alexander CM, Amiel SA, et al. Continuous glucose monitoring and metrics for clinical trials: an international consensus statement. *Lancet Diabetes Endocrinol.* 2023.
7. Wadwa RP, Reed ZW, Buckingham BA, et al. Trial of Hybrid Closed-Loop Control in Young Children with Type 1 Diabetes. *N Engl J Med.* 2023;388(11):991-1001. PMCID: PMC10082994
8. Brown SA, Kovatchev BP, Raghinaru D, et al. Six-Month Randomized, Multicenter Trial of Closed-Loop Control in Type 1 Diabetes. *N Engl J Med.* 2019;381(18):1707-1717. PMCID: PMC7076915
9. Ware J, Allen JM, Boughton CK, et al. Randomized Trial of Closed-Loop Control in Very Young Children with Type 1 Diabetes. *N Engl J Med.* 2022;386(3):209-219.
10. Bionic Pancreas Research Group. Multicenter, Randomized Trial of a Bionic Pancreas in Type 1 Diabetes. *New England Journal of Medicine.* 2022;387(13):1161-1172.