ARIC Publication Admin Use Only: ARIC Manuscript Proposal #4360

ARIC Publication Admin Use Only: PC Reviewed: 11/21/23

1.a. Full Title: **Glucose abnormalities detected by continuous glucose monitoring in older adults with prediabetes**

b. Abbreviated Title (Length 26 characters): **CGM and prediabetes**

2. Writing Group [please provide a middle name if available; EX: Adam Lee Williams]:

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I, the first author, confirm that all the coauthors have given their approval for this manuscript proposal. _NRD____ **[please confirm with your initials electronically or in writing]**

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3. Timeline: All data is currently available. Data analysis to begin after approval of this manuscript proposal.

4. Rationale:

Prediabetes is common in older adults, however, the optimal way to screen for prediabetes in older populations is controversial. The standard approach to diagnose prediabetes is based on a hemoglobin A1c (HbA1c) between 5.7% and 6.4% or a fasting plasma glucose between 100 mg/dL and 125 mg/dL. However, some guidelines recommend screening all older adults ages 65 years and older who have an HbA1c or fasting glucose in the prediabetic range, with a two-hour oral glucose tolerance test (OGTT) to identify cases of prediabetes not captured by the traditional tests.[1] It has been estimated that the cost of screening all older adults with prediabetic levels of HbA1c or fasting glucose with an OGTT would be between $737 million and $1.7 billion.[2] In addition to the financial costs, OGTTs are burdensome for vulnerable older adults who likely have comorbidities. The number of older adults who would be classified as having diabetes based on an elevated OGTT (≥200 mg/dL) would increase substantially, however, these same individuals would not be eligible for medication due to their non-diabetic HbA1c levels.

The extent of undetected hyperglycemia in older adults who are diagnosed with prediabetes based on traditional tests is poorly understood. Continuous glucose monitoring (CGM) is a minimally invasive state-of-the-art technology that measures glucose in interstitial fluid. CGM provides insight into glucose patterns and variability not reflected in a single fasting glucose or HbA1c measure. There is evidence that glycemic variability, or the oscillation between high and low levels of glucose, contributes to the risk of complications among persons with diabetes, independent of glucose and hemoglobin A1c (HbA1c).[3,4] Understanding the glucose patterns and glycemic variability in older adults with prediabetes can guide clinicians in determining whether additional screening of individuals with prediabetes is warranted.

Few studies worldwide have looked at CGM in older adults with prediabetes.[5-8] Our proposed study will examine the prevalence of standard CGM-defined glucose abnormalities and variability in >1200 older adults (with normoglycemia, prediabetes or diabetes) who participated in the Atherosclerosis Risk in Communities Study. Specifically, we will focus on characterizing and comparing glycemic variability and frequency of abnormalities in persons with prediabetes as it relates to glucose patterns among persons with normoglycemia or diabetes. Relatively low or normal glycemic variability and frequency of abnormalities in persons with prediabetes would refute guidelines which recommend further screening these individuals with an OGTT.

5. Main Hypothesis/Study Questions:

Aim 1: To characterize the prevalence of hyperglycemia and other abnormal glucose patterns in older adults with prediabetes using CGM sensors.

Hypothesis 1: CGM data will reveal that the prevalence of undetected glucose abnormalities (including high glycemic variability and episodes of hyperglycemia) in older adults with prediabetes based on HbA1c (5.7-6.4%) is low and similar to those with normoglycemia.

6. Design and analysis

a) Study design

Cross-sectional study at visit 9 (2021-2022)

b) Inclusion/exclusion criteria

- Older adults who participated in Visit 9 (2021-22) of the Atherosclerosis Risk in Communities (ARIC) Study and wore a CGM for up to 2 weeks.
- Participants were excluded from the ARIC Visit 9 CGM protocol if they had a history of allergic skin reaction to adhesive tape, could not commit to 2 weeks of monitoring, or had an implantable device (e.g., pacemaker).

c) Exposure

- Prediabetes will be defined as an HbA1c 5.7-6.4%
- Normoglycemia will be defined as an HbA1c <5.7%
- Diabetes will be defined as an HbA1c ≥6.5% (i.e., undiagnosed diabetes), self-reported diagnosis of diabetes between visits 6 and 9, or self-reported diabetes medication use between visits 5 and 9

Outcome

Abbott FreeStyle Libre Pro CGM

The Abbott FreeStyle Libre Pro CGM system was used to measure glucose for up to 14 days in all participants who consented to wearing the CGM. This system is factory calibrated (no finger stick needed), records interstitial glucose every 15 minutes and stores the 14 days of data. Participants were masked to the glucose readings.

We will consider the following CGM-defined metrics:

- ***Mean glucose***
  - Average of all available glucose measurements
- ***Glycemic variability***
  - coefficient of variation (CV)
  - standard deviation (SD)
- ***Time-in-range***
  - 70-140 mg/dL
  - 70-180 mg/dL
- ***Hypoglycemia***
  - Episodes- sustained glucose <70 mg/dL for at least 15 minutes during the 2-week period
  - Number of minutes spent <70 mg/dL as a percentage of the total length of time that the sensor was worn
- ***Hyperglycemia***

- Episodes- sustained glucose >140 mg/dL (Level 1) or >180 mg/dL (Level 2) for at least 15 minutes during the 2-week period
- Number of minutes spent above these thresholds as a percentage of the total length of time that the sensor was worn
- Area under the curve (AUC) of hyperglycemic excursion
- Mean amplitude of glycemic excursions (MAGE)

d) Summary of data analysis

We will plot the distributions of CGM-defined metrics (i.e., mean glucose, CV) by diabetes status (normoglycemia, prediabetes, diabetes).

We will use t-tests and χ^2 tests to compare CGM-defined metrics (i.e., mean glucose, CV, SD, time-in-range) and the prevalence of abnormalities (i.e., time in hyperglycemia, time in hypoglycemia) between those with prediabetes compared to (1) those with normoglycemia, and (2) those with diabetes.

We will graph ambulatory glucose profiles (over the maximum of 14 days of wear) by diabetes status with Tukey smoothing and plotting of the 5^{th}, 25^{th}, 50^{th}, 75^{th} and 95^{th} percentiles.

Sensitivity analyses

We will re-run the analyses using derived CGM metrics for daytime hours and nighttime hours separately as well as by days of the week, to examine if glucose profiles vary by these aspects. Additionally, CGM-detected hypoglycemia during sleep may be due to compression so analyzing the data by daytime hours vs. nighttime hours will help elucidate true episodes of hypoglycemia.

We will also conduct sensitivity analyses excluding values during the first 24 hours of the CGM sensor wear period (warm up time).

e) Limitations

- Primarily white and black participants
- Participants may have altered their eating habits while being monitored which would affect their typical glucose profiles
- The reliability of the CGM at low levels is weaker than at higher levels. The Abbott FreeStyle Libre sensor tends to overestimate the degree of hypoglycemia compared with venous glucose.

f) Will the author need Limited data to complete the proposed manuscript? ☐ Yes, Limited data is needed. ☒ No, De-identified data will be sufficient.

*Please note, Limited dataset access is strict and rarely provided. Limited data includes identifiable information such as dates (birthdays, visit dates, etc.). CMS, Genomic, Geocoded, and Proteomics/Somalogic data all fall under the limited data category. De-identified data does not include dates. All dates are date adjusted to "Days since Visit 1".

7.a. Will the data be used for non-ARIC analysis or by a for-profit organization in this manuscript? ☐ Yes ☒ No

b. If Yes, is the author aware that the current derived consent file ICTDER05 must be used to exclude persons with a value RES_OTH and/or RES_DNA = "ARIC only" and/or "Not for Profit" ? ☐ Yes ☐ No
(The file ICTDER is distributed to ARIC PIs annually, and contains the responses to consent updates related to stored sample use for research.)

8.a. Will the DNA data be used in this manuscript? ☐ Yes ☒ No

8.b. If yes, is the author aware that either DNA data distributed by the Coordinating Center must be used, or the current derived consent file ICTDER05 must be used to exclude those with value RES_DNA = "No use/storage DNA"? ☐ Yes ☐ No

9. The lead author of this manuscript proposal has reviewed the list of existing ARIC Study manuscript proposals and has found no overlap between this proposal and previously approved manuscript proposals either published or still in active status.
ARIC Investigators have access to the publications lists under the Study Members Area of the web site at: https://aric.cscc.unc.edu/aric9/proposalsearch [ARIC Website→Publications→Proposal Search]

☒ Yes ☐ No

10. What are the most related manuscript proposals in ARIC (authors are encouraged to contact lead authors of these proposals for comments on the new proposal or collaboration)?

ARIC Manuscript Proposal #3792: Glucose Patterns in Older Adults: A Pilot Study in a Community-based Population

ARIC Manuscript Proposal #4172: Associations between Physical Activity and Continuous Glucose Monitoring Metrics in Older, Community-Dwelling Adults: The Atherosclerosis Risk in Communities (ARIC) Study

11.a. Is this manuscript proposal associated with any ARIC ancillary studies or use any ancillary study data? _☒ _ Yes ☐ No

11.b. If yes, is the proposal

☒ **A. primarily the result of an ancillary study (list number* _** 2019.28**_)**

☐ **B. primarily based on ARIC data with ancillary data playing a minor role (usually control variables; list number(s)* _____)**

*ancillary studies are listed by number
https://aric.cscc.unc.edu/aric9/researchers/ancillary_studies/approved_ancillary_studies [ARIC Website→Ancillary Studies→Approved Ancillary Studies]

12a. Manuscript preparation is expected to be completed in one to three years. If a manuscript is not submitted for ARIC review at the end of the 3-years from the date of the approval, the manuscript proposal will expire.

12b. The NIH instituted a Public Access Policy in April, 2008 which ensures that the public has access to the published results of NIH funded research. It is **your responsibility to upload manuscripts to PubMed Central** whenever the journal does not and be in compliance with this policy. Four files about the public access policy from http://publicaccess.nih.gov/ are posted in https://aric.cscc.unc.edu/aric9/publications/policies_forms_and_guidelines [ARIC WebsiteàPublicationsàPublication Policies, Forms, and Guidelines]. http://publicaccess.nih.gov/submit_process_journals.htm shows you which journals automatically upload articles to PubMed central.

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