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Continuous glucose monitoring metrics for earlier identification of pre-diabetes: protocol for a systematic review and meta-analysis

Sara Gottfried ,[1] Laura Pontiggia,[2] Andrew Newberg,[1] Gregory Laynor ,[3] Daniel Monti[1]

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[1]Department of Integrative Medicine and Nutritional Sciences, Thomas Jefferson University Hospitals, Philadelphia, Pennsylvania, USA
[2]Institute of Emerging Health Professions (IEHP), College of Health Professions, Thomas Jefferson University Hospitals, Philadelphia, Pennsylvania, USA
[3]New York University Health Sciences Library, NYU Grossman School of Medicine, New York, New York, USA

Correspondence to
Dr Sara Gottfried;
sara.gottfried@jefferson.edu

ABSTRACT

Introduction Glycaemic variability and other metrics are not well characterised in subjects without diabetes. More comprehensive sampling as obtained with continuous glucose monitoring (CGM) may improve diagnostic accuracy of the transition from health to pre-diabetes. Our goal is to investigate the glycaemic system as it shifts from health to pre-disease in adult patients without diabetes using CGM metrics. New insights may offer therapeutic promise for reversing dysglycaemia more successfully with dietary, nutritional and lifestyle change before progression occurs to pre-diabetes and diabetes.

Methods and analysis This systematic review will include comprehensive searches of the PubMed, Scopus, Cochrane Library and ClinicalTrials.gov databases, with restrictions set to studies published in the last 10 years in English and planned search date 10 March 2022. Reference lists of studies that meet eligibility criteria in the screening process will subsequently be screened for the potential inclusion of additional studies. We will include studies that examine CGM use and report diagnostic criteria such as fasting glucose and/or haemoglobin A1c such that we can assess correlation between CGM metrics and established diagnostic criteria and describe how CGM metrics are altered in the transition from health to pre-diabetes. The screening and data extraction will be conducted by two independent reviewers using Covidence. All included papers will also be evaluated for quality and publication bias using Cochrane Collaboration risk of bias tools. If there are two or more studies with quantitative estimates that can be combined, we will conduct a meta-analysis after assessing heterogeneity.

Ethics and dissemination The systematic review methodology does not require formal ethical review due to the nature of the study design. Study findings will be publicly available and published in a peer-reviewed journal.

PROSPERO registration number CRD42022308222.

STRENGTHS AND LIMITATIONS OF THIS STUDY

⇒ To our knowledge, this will be the first systematic review and meta-analysis to compare continuous glucose monitoring metrics with the gold standard for diagnosis of health or pre-diabetes in a population without diabetes.
⇒ The evidence is determined through a systematic search in four biomedical databases and targeted searching of the grey literature in relevant conference proceedings.
⇒ The Covidence systematic review software will be used for blinded screening, conflict resolving, data extraction and quality assessment by three independent reviewers.
⇒ The Cochrane Collaboration risk of bias tools will be used for evaluating quality and risk of bias.
⇒ Limitations include a bias for studies published in English in the past 10 years, with adult subjects in age range from 18 to 65 years.

INTRODUCTION

Rates of pre-diabetes and diabetes continue to increase in prevalence. Pre-diabetes affects 88 million adults, more than one in three US adults.[1] However, most people with pre-diabetes are undiagnosed or unaware. Pre-diabetes is thought to be an intermediate state of hyperglycaemia with glycaemic parameters above normal but below the diabetes threshold. Further, the gold standard of blood sugar measurement from the American Diabetes Association—fasting glucose, glycosylated haemoglobin (haemoglobin A1c or HbA1c) and oral glucose tolerance testing in response to a 75-gram glucose load[2]—is limited because they diagnose dysglycaemia late in the pathophysiological process when it may be more difficult to reverse. Pre-diabetes represents worsening fasting glucose and/or impaired glucose tolerance, but definitions vary, leading to significant practice disparity and low guideline adherence.[3] Additionally, there are racial and gender disparities in pre-diabetes screening.[4]

Glycaemic variability and other continuous glucose monitoring (CGM) metrics are not well characterised in subjects without diabetes. Normal glucose (euglycaemia) variability on a moment-to-moment basis

has yet to be elucidated. Most standards of euglycaemia rely on targets from epidemiological studies of episodic measurement, which document clinical labs measured annually rather than a more comprehensive characterisation of the individual's glycaemic status. People with similar HbA1c and mean glucose show extremely different daily glucose excursions and variability, leading to debate and lack of consensus about pathophysiological pathways in the gradient from health to disease.[5] Indeed, standard measurements like HbA1c are limited because several conditions affect reliability, including patient ethnicity; conditions that impair erythrocyte production or alter the normal process of glycation; and even normal ageing.[6 7] Moreover, fasting glucose of 100 mg/dL may not be sufficient to separate individuals with normoglycaemia from individuals with pre-diabetes. Subjects with fasting glucose less than 100 mg/dL show impaired glucose tolerance when monitored continuously for at least 24 hours.[8] Subjects who are morbidly obese and euglycaemic have higher glycaemic variability compared with subjects with normal weight and without diabetes.[9] Some investigators use a fasting plasma glucose level ≤5.4 mmol/L (97 mg/dL) after an overnight fast because it has greater sensitivity to exclude diabetes in the absence of an oral glucose tolerance test (OGTT).[10] Evidence supports increased insulin resistance and up to a threefold greater risk of diabetes when fasting glucose exceeds 90 mg/dL.[11]

Excess glycaemic variability, especially postprandial, triggers increased oxidative stress that can damage tissues, such as blood vessels.[12–14] Glycaemic variability within the gold standard of 'normal' may raise cardiovascular risk and precede an increase in HbA1c.[15] Glycaemic variability may modulate cardiovascular risk even when fasting glucose and A1c are normal.[16] While most of the data on downstream damage from excess glucose excursions are derived from patients with diabetes, the scientific literature increasingly indicates that microvascular and macrovascular complications may occur in subjects without diabetes.[16–18] Risk may be higher in women at lower glucose levels compared with men.[19 20] Evidence shows that characterising dysglycaemia with greater precision uncovers higher cardiometabolic risk associated with specific glucose derangements such as postprandial hyperglycaemia,[21 22] acute glucose spikes[23 24] and perhaps nocturnal hypoglycaemia.[25–28] From a systems biology perspective, the convention of single or limited series measurement of glucose testing may be inadequate to detect downstream dysfunction, setting the stage for more dense sampling and real-world evidence as obtained with CGM and potentially better diagnostic accuracy.[29]

Our goal is to interrogate the glycaemic system as it shifts from health to pre-disease in patients without diabetes using CGM metrics. New insights may offer therapeutic promise for reversing dysglycaemia more successfully with dietary, nutritional and lifestyle change before progression occurs to pre-diabetes and diabetes.

Objectives

This systematic review aims to answer the following questions:

1. How do CGM metrics differ between euglycaemia and pre-diabetes?
2. What is the relation (correlation) between CGM dynamic metrics and established diagnostic criteria?
3. What is the diagnostic power of CGM dynamic metrics?

METHODS AND ANALYSIS

The protocol for the present systematic review and meta-analysis follows the Preferred Reporting Items for Systematic Review and Meta-Analysis Protocols guidelines,[30] and the Cochrane Handbook of Systematic Reviews of Interventions.[31]

The protocol is registered with the National Institute for Health Research International Prospective Register of Systematic Reviews (CRD42022308222).

Eligibility criteria

A summary of the participants, interventions, comparators and outcomes considered, as well as the type of studies included according to PICOS strategy,[32] is provided below.

Population

The target population is adults (> 18 years old) who are diagnosed with pre-diabetes (fasting glucose 100–125 mg/dL after a minimum 8-hour fast, and/or HbA1c 5.7–6.4%, and/or 2-hour OGTT with glucose 140–199 mg/dL) as defined by the American Diabetes Association (https://www.diabetes.org/a1c/diagnosis, accessed 24 January 2022). We will use the criteria of fasting glucose 100–125 mg/dL or HbA1c of 5.7–6.4% since the 2-hour OGTT is less commonly used in clinical practice, but we will extract the data if available. In order to create the most homogeneous pool of studies to address our research questions in adults without diabetes, studies that include only participants under the age of 18 years, above the age of 65 years, or diagnosed with type 1 and/or type 2 diabetes will be excluded. Studies will also be excluded if focused on subjects with acute illness or systemic chronic disease (eg, liver, kidney, stroke, coronary artery disease).

Intervention

We will evaluate primary studies that report outcomes of the use of CGM in patients with pre-diabetes and/or healthy subjects.

Comparison

Potentially relevant CGM biomarkers are identified by comparing pre-diabetes values with values for healthy controls (fasting glucose <100 mg/dL, and/or HbA1c <5.7%, and/or 2-hour OGTT with glucose <140 mg/dL).

CGM biomarkers are then compared with standard diagnostics for pre-diabetes.

Outcomes

In order to explore and define novel CGM biomarkers to predict transition from normal to pre-diabetic phenotype, the following outcomes are considered:

- CGM metrics include but are not limited to the following: mean, standard deviation (SD), coefficient of variation (CV), continuous overall net glycaemic action (CONGA), mean amplitude of glycaemic excursions (MAGE), mean absolute glucose (MAG), glycaemic assessment diabetes equation (GRADE), % time in range, % time below range, % time above range (note that the definition of time in range may vary by author, which will be addressed in the systematic review).
- Pearson correlation coefficient and results of error grid analysis between the CGM system metrics and established glucose monitoring methods (fasting glucose, HbA1c, 2-hour OGTT).
- CGM metrics diagnostic power (eg, sensitivity, specificity, area under the curve, diagnostic OR).

Study design

This review includes observational (eg, case report, case series, cross-sectional, case–control, cohort) and interventional (eg, quasi-experimental studies, randomised controlled trials, community trials, field trials) primary, peer-review studies in which CGM is the only intervention under investigation. We will exclude reviews, editorials, commentaries, letters, opinions, meta-analysis, case reports, conference abstracts, comments, preclinical (in vitro; animal model) studies and clinical trials involving additional interventions. Studies will be restricted to the English language and published in the last 10 years, since for technologies that evolve and improve rapidly, like CGM, the more recent studies (using the technology closer to the current one) are majorly relevant.

Search methods for identifying studies

Sources of studies

We will conduct systematic searches of the PubMed, Scopus, Cochrane Library and ClinicalTrials.gov databases. Searches will be limited to studies published in English within 10 years of the time of conducting the search. We will additionally search for unpublished studies in grey literature, by reviewing abstracts from a targeted group of conference proceedings for potential inclusion of additional studies. When available, the proceedings of these conferences from 2012 to 2022 will be searched: Precision Nutrition and Metabolism Conference; Harvard Precision Medicine Annual Conference; International Precision Medicine Conference and Precision Medicine World Conference.

Search strategy

A medical librarian on the review team developed a comprehensive search strategy encompassing the aims of the systematic review. The strategy combines four sets of terms with Boolean operators: (1) terms related to pre-diabetes; (2) terms related to CGM; (3) terms related to diagnostic criteria for pre-diabetes; and (4) terms related to diagnostic accuracy and the prediction of transition. Each set of terms includes both keywords searched in the title/abstract field and database-specific subject headings. Terms within each set are combined with the operator OR. The four sets of terms are then combined with the operator AND, yielding studies that include at least one term from each set. The initial search strategy was developed in PubMed (see online supplemental file 1). The strategy will be translated into the other included databases, using appropriate subject headings for each database.

Study selection

All records identified in the database search will be uploaded to Covidence systematic review software (https://www.covidence.org) for automatic deduplication and blinded screening, conflict resolving, study selection and data extraction. Two authors will independently perform the initial primary article screening based on the information contained in their titles and abstracts, and categorise them into three groups: relevant, irrelevant and unsure. In case of disagreement, the article will be re-evaluated and, if the disagreement persists, a third reviewer will make a final decision. Full-paper screening will then be conducted by the same independent investigators and a list of articles to be included in the review is compiled. Reference lists of articles that meet eligibility criteria in the screening process will subsequently be screened for potential inclusion of additional studies.

Data extraction

Two independent authors will extract data from the final studies identified as eligible to be included in the review using a predesigned pilot-tested data collection form using the Covidence extraction module. Eventual discrepancies will be addressed with a third reviewer and discussed until consensus is reached.

The data to be extracted will include:

1. Publication details: authors, title, journal, year of publication, country in which the study was conducted and funding source(s).
2. Study design: type of study, inclusion and exclusion criteria, method of recruitment of participants, limitations and mitigation strategies.
3. Participant details: sample size, demographic information (eg, age, gender, comorbidities).
4. Intervention characteristics: CGM device brand and model, CGM duration and aim of intervention.
5. Study outcomes: CGM metrics, correlation between CGM metrics and established diagnostic criteria.

In cases of missing, incomplete or unclear data in the included studies, we will attempt to contact study authors for further information.

Risk of bias

The Cochrane Collaboration risk of bias tools will be used to assess the risk of bias in the studies that meet inclusion criteria.[33–35] This will be assessed independently by two reviewers, with conflicts resolved by a third reviewer.

Data synthesis and analysis

Data will be entered into a custom database and a narrative synthesis will summarise the findings of the review by organising data into a systematic narrative review, tables and figures of data extraction. For continuous outcomes, analysis will be performed using standardised mean differences or mean differences with its respective 95% CIs. Binary outcomes will be analysed and reported using risk ratio or OR with its respective 95% CIs. Studies with similar characteristics and outcomes will be grouped and, where suitable data and homogeneity exist, a meta-analysis will be performed using random-effects models. A combined Pearson correlation coefficient between CGM metrics and established diagnostic criteria (ie, fasting plasma glucose, HbA1c, 2-hour OGTT) with 95% CI will also be calculated. If sufficient data are available, subgroup analysis will be carried out to explore CGM metrics estimates for pre-diabetes stratified by age, sex, race and ethnicity, type of CGM device and body mass index.

Patient and public involvement

As this research will be based on previously published data, there will be no patient and public involvement in the design, interpretation or dissemination of the findings.

DISCUSSION

This systematic review will provide important information about the benefits of adding CGM to standard diagnostic measures in the diagnosis of euglycaemia versus pre-diabetes. Currently, there are many challenges that exist with the diagnosis of pre-diabetes.[36] The technology, emerging algorithms and more comprehensive data set have shown promise distinguishing subjects with euglycaemia from subjects with pre-diabetes at an earlier stage, and likely before standard measures such as HbA1c show abnormalities. Previously, Hall *et al* discovered that in individuals considered to be euglycaemic by single or episodic measurement, CGM identifies an additional 15% of patients with pre-diabetes and 2% with diabetes, suggesting that dysglycaemia is more prevalent than previously understood and that CGM metrics may be a more sensitive indicator of dysglycaemia, though the cost is certainly higher.[29] The findings will inform further work that will aim to more fully characterise the stages in the transition from health to pre-diabetes, potentially providing a mechanism for patients to be more involved and empowered to reverse dysglycaemia in response to food and lifestyle factors. There are several limitations to the current review protocol. The review will be restricted to published studies in the last 10 years, which introduces publication bias. Second, only studies written in English language will be included, introducing language bias. Third, we acknowledge that CGM values in subjects without diabetes are not linked with hard outcomes like retinopathy or nephropathy, so that the clinical relevance of our findings will remain associative only. Finally, we note that CGM has not been validated by any health agency for any form of diabetes or non-diabetes and that the identified CGM metrics are exploratory.

ETHICS AND DISSEMINATION

Owing to the study design of systematic reviews and meta-analyses, ethics approval is not necessary. The systematic review will be published in a peer-reviewed journal and presented at appropriate conferences. This protocol will be adapted for the analysis of other classes of biomarkers for pre-diabetes.

Contributors SG was involved in conceptualisation, methodology, preliminary systematic review, formal analysis, writing and revising the protocol manuscript, study supervision and project administration. LP was involved in project conception and development, methodology, preliminary systematic review, formal analysis, study supervision, acquisition of data, data analysis, and writing and revising the protocol. AN was involved in conceptualisation, study supervision, and writing and revising the manuscript. GL was involved in systematic review search strategy development, registration of the protocol in PROSPERO and writing of the protocol manuscript. DM was involved in project conception and development, and writing the protocol manuscript. All authors read and approved the final manuscript.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting, or dissemination plans of this research.

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ORCID iDs

Sara Gottfried http://orcid.org/0000-0002-0606-1184
Gregory Laynor http://orcid.org/0000-0002-4578-4051

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