BMJ Open Diabetes Research & Care

Role of 2-hour plasma glucose in assessing pre-diabetes risk: insights from the vitamin D and type 2 diabetes (D2d) study cohort

Sun H Kim ,[1] Vanita R Aroda ,[2] Ranee Chatterjee,[3] Erin S LeBlanc ,[4] Jason Nelson,[5] Neda Rasouli ,[6] Myrlene A Staten,[7] Ellen M Vickery,[8] Anastassios G Pittas,[8] Daniel S Hsia[9]

To cite: Kim SH, Aroda VR, Chatterjee R, *et al*. Role of 2-hour plasma glucose in assessing pre-diabetes risk: insights from the vitamin D and type 2 diabetes (D2d) study cohort. *BMJ Open Diab Res Care* 2025;13:e004953. doi:10.1136/bmjdrc-2025-004953

► Additional supplemental material is published online only. To view, please visit the journal online (https://doi.org/10.1136/bmjdrc-2025-004953).

Received 27 January 2025
Accepted 4 February 2025

For numbered affiliations see end of article.

Correspondence to
Dr Sun H Kim;
sunhkim@stanford.edu

Historically, an elevated level of 2-hour plasma glucose (2hPG) during a 75-gram oral glucose tolerance test (OGTT) was the hallmark of pre-diabetes. This measurement served as a primary criterion in pivotal diabetes prevention clinical trials, including the Diabetes Prevention Program.[1] However, with the American Diabetes Association (ADA) expanding its diagnostic criteria for pre-diabetes in 2010 to include hemoglobin A1c (HbA1c),[2] clinical practice has shifted from measuring 2hPG to relying primarily on fasting plasma glucose (FPG) and HbA1c.[3] This transition raises questions about the current role of 2hPG in assessing pre-diabetes risk in contemporary clinical settings.

The vitamin D and type 2 diabetes (D2d) study was a randomized, double-blind, placebo-controlled clinical trial that tested whether oral vitamin D lowers the risk of developing diabetes in adults at risk of type 2 diabetes (clinicaltrials.gov NCT 01942694).[4] Participants were eligible if they had "high-risk" pre-diabetes, which was defined as meeting 2 or 3 ADA glycemic criteria for pre-diabetes (FPG, 100–125 mg/dL; 2hPG, 140–199 mg/dL; HbA1c, 5.7–6.4%).[5] Diabetes was diagnosed based on semiannual glycemic testing.

Analyzing the placebo cohort only, we found that 26.7% of participants (323 out of 1212) developed diabetes after a median follow-up of 2.5 years. More men than women developed diabetes (29% vs 23%, p=0.02), but other demographic factors were similar, including age, race, and ethnicity (online supplemental table 1). To examine the diagnostic value of 2hPG in conjunction with FPG and HbA1c for predicting incident diabetes, we compared the area under the receiver-operating characteristic curves (ROC AUC). With only FPG and HbA1c, the ROC AUC to predict incident diabetes at 36 months was 0.686. Adding 2hPG to FPG and HbA1c increased the ROC AUC to 0.736 (p=0.002), improving the performance of glycemic measures to predict incident diabetes.

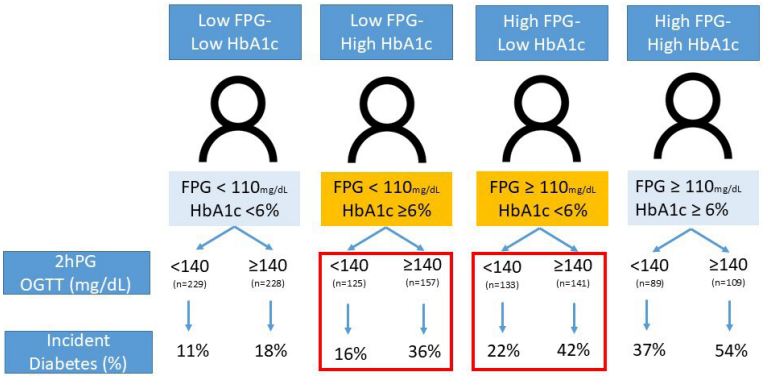

Figure 1 Added benefit of the 2hPG value in predicting diabetes in a pre-diabetes population stratified by FPG and HbA1c. One participant in the low FPG-low HbA1c was missing a 2hPG value. 2hPG, 2-hour plasma glucose; FPG, fasting plasma glucose; HbA1c, hemoglobin A1c.

We subsequently examined which subpopulations defined by FPG and HbA1c would benefit from adding 2hPG values (figure 1). We categorized participants based on FPG (<110 or ≥110 mg/dL) and/or HbA1c (<6 or ≥6%) into four subgroups: low FPG-low HbA1c, low FPG-high HbA1c, high FPG-low HbA1c, and high FPG-high HbA1c. Incidence rates of diabetes within these subgroups were 14.4%, 27.0%, 32.1%, and 46.5%, respectively. Further stratification based on 2hPG values revealed that meeting the pre-diabetes criterion for 2hPG substantially increased the cumulative incidence of diabetes. Specifically, individuals with low FPG-high HbA1c and high FPG-low HbA1c who also had 2hPG in the pre-diabetes range had the greatest increase, with diabetes development percentages increasing from 16% to 36% and from 22% to 42%, respectively.

If we consider a cumulative risk of ≥25% over 2.5 years (≥10% per year) as "very high risk," individuals with low FPG and low HbA1c would not meet this threshold even when 2hPG is ≥140 mg/dL. Conversely, those with high FPG and high HbA1c surpassed this threshold regardless of their 2hPG level. However, in the other groups—low FPG-high HbA1c or high FPG-low HbA1c—meeting the 2hPG pre-diabetes criterion shifted their risk classification from "high" to "very high."

Despite the high prevalence of pre-diabetes, the clinical progression and diabetes risk among individuals vary significantly.[6] In our study, the cumulative risk for diabetes varied substantially, from 11% to 54%, based on different glycemic criteria (figure 1). Importantly, using 2hPG was especially effective for categories with incongruent FPG and HbA1c values (low FPG-high HbA1c or high FPG-low HbA1c), allowing for a more precise determination of whether individuals fell into the "high" or "very high" risk brackets. Our findings indicate that integrating 2hPG into the assessment enhances the predictive performance of diabetes in a contemporary cohort at risk for type 2 diabetes. Therefore, 2hPG remains a valuable tool in clinical medicine and may be selectively used to refine diabetes risk profiles.

Author affiliations
[1]Division of Endocrinology, Gerontology, and Metabolism, Stanford University School of Medicine, Stanford, California, USA
[2]Division of Endocrinology, Diabetes and Hypertension, Brigham and Women's Hospital, Harvard Medical School, Boston, Massachusetts, USA
[3]Department of Medicine, Duke University School of Medicine, Durham, North Carolina, USA
[4]Kaiser Permanente Center for Health Research, Portland, Oregon, USA
[5]Tufts CTSI, BERD Center, Tufts Medical Center, Boston, Massachusetts, USA
[6]Division of Endocrinology, Metabolism and Diabetes, University of Colorado School of Medicine and VA Eastern Colorado Health Care System, Aurora, Colorado, USA
[7]NIDDK (Retired), Bethesda, Maryland, USA
[8]Division of Endocrinology, Diabetes and Metabolism, Tufts Medical Center, Boston, Massachusetts, USA
[9]Pennington Biomedical Research Center, Baton Rouge, Louisiana, USA

Acknowledgements The authors thank the D2d investigators, staff, and trial participants for their outstanding dedication and commitment to the study.

AGP is supported in part by generous donations to the Tupper Research Fund at Tufts Medical Center. SHK is partially funded by the Bose Family Fund and P30DK116074.

Contributors SHK, AGP, and DSH were involved in the conception and design of the study. JN performed the statistical analyses, and all authors were involved in the interpretation of the results. SHK wrote the first draft of the letter, and all authors edited, reviewed, and approved the final version of the manuscript. SHK is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Funding The D2d study was primarily funded by NIDDK (U01DK098245) and secondarily by the American Diabetes Association (1-14-D2d-01).

Competing interests None declared.

Patient consent for publication Not applicable.

Ethics approval The D2d study involved collaboration among 22 academic medical centers in the United States. The institutional review boards at each clinical site approved the protocol (https://d2dstudy.org/sites). Participants gave informed consent to participate in the study before taking part.

Provenance and peer review Not commissioned; internally peer reviewed.

Data availability statement Data are available upon reasonable request. Data described in the manuscript, code book, and analytic code are not publicly available but will be made available from the D2d Coordinating Center at Tufts Medical Center on reasonable request. Protocol synopsis, contact details, publications, and the process for collaboration and data requests can be found on the website (d2dstudy.org).

ORCID iDs
Sun H Kim http://orcid.org/0000-0003-0895-7491
Vanita R Aroda http://orcid.org/0000-0002-7706-4585
Erin S LeBlanc http://orcid.org/0000-0002-4067-3432
Neda Rasouli http://orcid.org/0000-0003-1269-3580

REFERENCES

1 Knowler WC, Barrett-Connor E, Fowler SE, *et al*. Reduction in the incidence of type 2 diabetes with lifestyle intervention or metformin. *N Engl J Med* 2002;346:393–403.
2 American Diabetes Association. Diagnosis and classification of diabetes mellitus. *Diabetes Care* 2010;33:S62–9.
3 Evron JM, Herman WH, McEwen LN. Changes in Screening Practices for Prediabetes and Diabetes Since the Recommendation for Hemoglobin A_{1c} Testing. *Diabetes Care* 2019;42:576–84.
4 Pittas AG, Dawson-Hughes B, Sheehan P, *et al*. Vitamin D Supplementation and Prevention of Type 2 Diabetes. *N Engl J Med* 2019;381:520–30.
5 ElSayed NA, McCoy RG, Aleppo G, *et al*. 2. Diagnosis and Classification of Diabetes: Standards of Care in Diabetes—2025. *Diabetes Care* 2025;48:S27–49.
6 Richter B, Hemmingsen B, Metzendorf M-I, *et al*. Development of type 2 diabetes mellitus in people with intermediate hyperglycaemia. *Cochrane Database Syst Rev* 2018;10:CD012661.