Metabolism Open 10 (2021) 100091

Contents lists available at ScienceDirect

Metabolism Open

journal homepage: www.journals.elsevier.com/metabolism-open

Prediabetes screening: Questionable benefits in the golden years

Keywords:
Diabetes
Glycated hemoglobin
Glucose
Prediabetes
Screening

A B S T R A C T

Irrespective of the definition and diagnostic criteria used, the term prediabetes denotes a state of dysmetabolism with a high risk of progression to diabetes mellitus. Although diabetes-related complications may already be evident among individuals with prediabetes, interventions at this stage primarily aim to hinder the development of overt hyperglycemia rather than to prevent complications. Current recommendations for prediabetes testing are common across all adult age categories. Recent evidence arising from the prospective investigation of the natural course of prediabetes among elderly individuals pose questions regarding the benefits of meticulous prediabetes screening in this age group. In view of this and due to the lack of sufficient data to concretely support a positive impact of further preventive strategies among older individuals, screening recommendations should be reevaluated to target selected elderly individuals who are most likely to benefit in terms of quality of life and prognosis. Further therapeutic measures should be tailored to the inherent features of this frail age group, in order to exert a meaningful effect on overall health status.

Prediabetes is a term used to describe a state of metabolic dysregulation, which is distinguished by glucose levels above normal but lower than those diagnostic for diabetes mellitus (Table 1).

The latest estimates of the global prevalence of diabetes mellitus are in the range of 9.3% [1], while 1 out of 3 adults may fulfill the diagnostic criteria for prediabetes, although the latter is highly dependent on the used definition [2]. However, irrespective of definition, prediabetic states share a high probability of progression to type 2 diabetes mellitus (T2DM) [3]. Typical diabetes complications associated with chronic hyperglycemia, such as neuropathy, retinopathy, nephropathy and coronary artery disease may already be evident among patients with prediabetes [4–6]. Although there are ongoing randomized trials to address the issue of prevention of complications through antihyperglycemic therapy at this stage [7], the principal strategies in prediabetic populations aim towards the prevention of progression to T2DM through lifestyle modification and, to a lesser extent, drug therapy [8]. A diagnosis of prediabetes most often emerges during screening for T2DM, which is recommended for individuals with high-risk features, namely overweight or obesity plus one or more defined risk factors for dysglycemia (Table 1). Even though diabetes and prediabetes become more prevalent with older age and demographic aging is a prominent cause for the racing diabetes pandemic [9], current recommendations do not consider advanced age (or any particular adult age for that matter) as a compelling risk factor regarding DM screening. Furthermore, elderly individuals are often grossly underrepresented in clinical trials for diabetes therapy [10] or prevention [11]. As a result, many issues regarding prediabetes detection, management and prevention of DM are yet to be conclusively addressed.

In a recent publication in JAMA Internal Medicine [12], Rooney et al. followed up 3,412 elderly participants (mean age at recruitment 75.2 years, range 71–90 years, 60% female and 17% Black) without DM who participated in the ongoing Atherosclerosis Risk in Communities (ARIC) study. Participants were screened for the presence of prediabetes through fasting plasma glucose (FPG) and glycated hemoglobin (HbA1c) measurements using the criteria proposed by the American Diabetes Association (ADA), although the more stringent existing diagnostic cutoffs by the World Health Organization (WHO) and International Expert Committee (IEC) were used in secondary analyses. The development of T2DM was the primary outcome of the study, which was assessed after a median follow-up of 5.0 years (range 0.1–6.5 years).

At baseline, 59% of participants had impaired glucose tolerance and 44% presented HbA1c levels in the prediabetic range according to the ADA criteria, with 73% fulfilling either and 29% both prediabetes-defining conditions. With the use of the stricter WHO and IEC definitions, the prevalence of prediabetes was substantially lower (23 and 15%, respectively).

The probability of progression to diabetes was substantially higher among those with prediabetes in comparison to those with normoglycemia at baseline but was nevertheless relatively

Abbreviations: ADA, American Diabetes Association; BMI, Body Mass Index; CVD, Cardiovascular disease; DCCT, Diabetes Control and Complications Trial; DM, Diabetes mellitus; FPG, Fasting plasma glucose; HbA1c, Glycated hemoglobin; HIV, Human immunodeficiency virus; IEC, International Expert Committee; NGSP, National Glycohemoglobin Standardization Program; oGTT, oral glucose tolerance test; PG, Plasma glucose; WHO, World Health Organization.

https://doi.org/10.1016/j.metop.2021.100091

Table 1
(A): Commonly used diagnostic criteria for prediabetes (including the equivalent diagnoses by the World Health Organization (WHO) and International Expert Committee (IEC) and diabetes mellitus based on glycemic cutoffs. (B) Criteria for diabetes/prediabetes screening in asymptomatic adults.

A. Diagnostic criteria[a] for prediabetes and diabetes mellitus

	ADA [15]		WHO [22]	IEC [23]
Laboratory variables	Prediabetes	DM	intermediate hyperglycemia	High risk for progression to DM
Fasting plasma glucose[b]	100–125 mg/dL (5.6–6.9 mmol/L)	≥126 mg/dL (7.0 mmol/L)	110–125 mg/dl (6.1–6.9 mmol/L)	
2h-PG (during oGTT)[c]	140–199 mg/dL (7.8–11.0 mmol/L)	≥200 mg/dL (≥11.1 mmol/L)		
Random PG and symptoms of hyperglycemia[d]		≥200 mg/dL (≥11.1 mmol/L)		
$HbA1_c$[e]	5.7–6.4% (39–47 mmol/mol)	≥6.5% (≥48 mmol/mol)		6.0–6.4% (42–47 mmol/mol)

B. Criteria for diabetes/prediabetes screening in asymptomatic adults

- BMI ≥25 kg/m^2 or ≥23 kg/m^2 in Asian Americans plus one or more of the following risk factors
- High-risk race/ethnicity (e.g., African American, Latino, Native American, Asian American, Pacific Islander)
- History of CVD
- First-degree relative with diabetes
- Hypertension
- Women with[a] polycystic ovary syndrome
- HDL cholesterol[b]levels35 mg/dL (0.90 mmol/L) and/or triglyceride levels >250 mg/dL (2.82 mmol/L)
- Physical inactivity
- Other clinical conditions associated with insulin resistance (e.g., severe obesity, acanthosis nigricans)
- HIV

[a] In the absence of unequivocal hyperglycemia, these criteria should be confirmed by repeat testing.
[b] Fasting is defined as no caloric intake for at least 8 hours.
[c] oGTT should be performed based on WHO guidelines with a glucose load containing the equivalent of 75g of anhydrous glucose dissolved in water.
[d] Random is defined as any time of day without regard to time since previous meal. The classic symptoms of hyperglycemia include polydipsia, polyuria and unexplained weight loss.
[e] Determination should be performed in a laboratory that is NGSP certified and standardized to the DCCT assay. Point-of-care assays should not be employed for diagnosis.

low (<12% regardless of the definition used), and in any case lower than the rate of regression to normoglycemia (44 and 13% for FPG- and HbA1c-defined prediabetes, respectively) or the risk of death (16 and 19%, respectively). Furthermore, the presence of prediabetes had no effect on mortality during the course of follow-up.

The results of the study may present a series of important implications in clinical practice. The first consideration would focus on the prognosis and natural history of prediabetes in this age group. There was a surprisingly high prevalence of prediabetes when either one of the ADA-proposed FPG or HbA1c criteria were fulfilled (73%), which was in stark contrast with the frequent regression to normoglycemia and the low rates of progression to diabetes mellitus. Since prediabetes regression was substantially more possible when it was based on FPG values, a reasonable assumption would attribute a part of initial diagnosis or follow-up reclassification to the low reproducibility of FPG, as the authors have accordingly discussed. It should be additionally taken into account that even though HbA1c exhibits a better degree of reproducibility between repeat measurements, a variety of hematological and other conditions that may contribute to the non-glycemic variability of HbA1c (and hence, compromises its usefulness as an indicator of glycemia and a screening test for prediabetes and diabetes) are inherently more prevalent among the elderly [13]. Repeated or combined measurements similarly to the recommended practice for DM diagnosis could aid to reduce false classifications, although the clinical yield and cost-effectiveness of such a strategy for prediabetes is unclear.

Second, setting a diagnosis of prediabetes currently serves to identify individuals at high-risk for progression to T2DM, so that adequate measures to prevent this outcome may come into action. Lifestyle modifications, namely weight loss and increase of physical activity, are the mainstay of preventive measures while metformin consists a reasonable alternative under given circumstances [14]. Although the efficacy of such preventive strategies in prediabetes has primarily been demonstrated among individuals with impaired glucose tolerance [15], and measurements of 2-h glucose were not available to be used for prediabetes diagnosis in the study by Rooney et al., the same recommendations apply irrespectively of the criterion used for prediabetes diagnosis. With respect to the population of interest, metformin use for the prevention of progression to DM is mainly encouraged among younger age groups (<60 years) [14]. Additionally, even though a loss of a certain minimum weight excess is recommended for all individuals with prediabetes and has a particular meaning among individuals with excess body weight, it should be considered that intentional or unintentional weight loss among elderly is associated with bone demineralization and increased fracture risk [16,17], which undoubtedly constitutes a major prognosis determinant in this population.

Furthermore, the probability of developing chronic diabetes complications is at least partially driven by the severity and duration of exposure to hyperglycemia, and conversely, the risk of treatment-related complications becomes higher with advancing age. Hence, it is not surprising that somewhat looser glycemic targets are recommended for elderly individuals with T2DM by most societies [18,19]. Although these targets may not be directly generalizable to untreated populations, they may be significant when implementing strategies for prediabetes screening and T2DM prevention. The same logic would apply when solid indications for antihyperglycemic therapy already in the state of prediabetes arise in the future for prevention of complications, on the basis of the results of ongoing clinical trials [7]. With respect to an expected shorter duration of exposure to hyperglycemia among individuals diagnosed in advanced age, a practice of routine medical therapy among elderly prediabetic individuals for prevention of “prediabetic” complications or progression to DM would seem, at the very best, questionable.

In summary, to ensure the cost-effectiveness and the “do good or do no harm” of health services regarding prediabetes and

T2DM, the practice of extensive DM screening among the elderly should be avoided, since the impact of this diagnosis and the optimal plan and risk/benefit balance of further management remains unclear. At best, primary care physicians should adhere to current screening recommendations in which age is not considered when assessing the risk of DM development. Particularly in this age group, this should be carried out under consideration of the aforementioned limitations of diagnostic tools. A preference for the use of the most stringent glycemic available cutoffs could theoretically aid to improve the yield of prediabetes detection among the elderly, although data to support this are presently lacking. Most importantly, screening should occur strictly after the physician has weighted that any preventive or therapeutic interventions that may arise based on screening results are likely to decisively affect patient prognosis and quality of life. Finally, regarding identified cases of prediabetes in this age group, further preventive strategies should focus on improving the overall health status, prognosis and quality of life of patients rather than explicitly target prevention of progression to T2DM. Towards that end, any medical therapy targeted for T2DM prevention would seem futile and is formally not recommended. Finally, regarding lifestyle interventions, measures to improve physical fitness and preserve muscle mass (for example, supervised aerobic or resistance training) could exert multifaceted beneficial health effects included but not limited to glucose metabolism [20,21] among older individuals, and should probably be preferred over weight-loss oriented approaches.

References

[1] Saeedi P, Petersohn I, Salpea P, Malanda B, Karuranga S, Unwin N, et al. Global and regional diabetes prevalence estimates for 2019 and projections for 2030 and 2045: results from the international diabetes federation diabetes atlas. Diabetes research and clinical practice. 9(th) edition 2019. 157:107843..

[2] Hostalek U. Global epidemiology of prediabetes - present and future perspectives. Clin. Diabetes.Endocrinol. 2019;5:5.

[3] Tabak AG, Herder C, Rathmann W, Brunner EJ, Kivimaki M. Prediabetes: a high-risk state for diabetes development. Lancet 2012;379:2279–90.

[4] Eleftheriadou A, Williams S, Nevitt S, Brown E, Roylance R, Wilding JPH, et al. The prevalence of cardiac autonomic neuropathy in prediabetes: a systematic review. Diabetologia 2021;64:288–303.

[5] Mutie PM, Pomares-Millan H, Atabaki-Pasdar N, Jordan N, Adams R, Daly NL, et al. An investigation of causal relationships between prediabetes and vascular complications. Nat Commun 2020;11:4592.

[6] Diabetes Prevention Program Research G. The prevalence of retinopathy in impaired glucose tolerance and recent-onset diabetes in the Diabetes Prevention Program. Diabet Med : J Br.Diabet. Assoc. 2007;24:137–44.

[7] Gabriel R, Boukichou Abdelkader N, Acosta T, Gilis-Januszewska A, Gomez-Huelgas R, Makrilakis K, et al. Early prevention of diabetes microvascular complications in people with hyperglycaemia in Europe. ePREDICE randomized trial. Study protocol, recruitment and selected baseline data. PloS One 2020;15:e0231196.

[8] Galaviz KI, Narayan KMV, Lobelo F, Weber MB. Lifestyle and the prevention of type 2 diabetes: a status report. Am J Lifestyle Med 2018;12:4–20.

[9] Kirkman MS, Briscoe VJ, Clark N, Florez H, Haas LB, Halter JB, et al. Diabetes in older adults. Diabetes Care 2012;35:2650–64.

[10] Cruz-Jentoft AJ, Carpena-Ruiz M, Montero-Errasquin B, Sanchez-Castellano C, Sanchez-Garcia E. Exclusion of older adults from ongoing clinical trials about type 2 diabetes mellitus. J Am Geriatr Soc 2013;61:734–8.

[11] Lindstrom J, Louheranta A, Mannelin M, Rastas M, Salminen V, Eriksson J, et al. The Finnish Diabetes Prevention Study (DPS): lifestyle intervention and 3-year results on diet and physical activity. Diabetes Care 2003;26:3230–6.

[12] Rooney MR, Rawlings AM, Pankow JS, Echouffo Tcheugui JB, Coresh J, Sharrett AR, et al. Risk of progression to diabetes among older adults with prediabetes. JAMA Intern Med. 2021;181(14):511–9.

[13] Wu L, Lin H, Gao J, Li X, Xia M, Wang D, et al. Effect of age on the diagnostic efficiency of HbA1c for diabetes in a Chinese middle-aged and elderly population: the Shanghai Changfeng Study. PloS One 2017;12:e0184607.

[14] American Diabetes A3. Prevention or delay of type 2 diabetes: standards of medical care in diabetes-2021. Diabetes Care 2021;44:S34–9.

[15] American Diabetes A2. Classification and diagnosis of diabetes: standards of medical care in diabetes-2021. Diabetes Care 2021;44:S15–33.

[16] Ensrud KE, Ewing SK, Stone KL, Cauley JA, Bowman PJ, Cummings SR, et al. Intentional and unintentional weight loss increase bone loss and hip fracture risk in older women. J Am Geriatr Soc 2003;51:1740–7.

[17] Jiang BC, Villareal DT. Weight loss-induced reduction of bone mineral density in older adults with obesity. J. Nutr.Gerontol. Geriatr. 2019;38:100–14.

[18] Leung E, Wongrakpanich S, Munshi MN. Diabetes management in the elderly. Diabetes Spectr : Publ.Am.Diabetes. Assoc 2018;31:245–53.

[19] American Diabetes A. 12. Older adults: standards of medical care in diabetes-2020. Diabetes Care 2020;43:S152–62.

[20] Langhammer B, Bergland A, Rydwik E. The importance of physical activity exercise among older people. BioMed Res Int 2018;2018:7856823.

[21] Koliaki C, Liatis S, Dalamaga M, Kokkinos A. Sarcopenic obesity: epidemiologic evidence, pathophysiology, and therapeutic perspectives. Current obesity reports 2019;8:458–71.

[22] Use of glycated haemoglobin (HbA1c) in the diagnosis of diabetes mellitus: abbreviated report of a WHO consultation. Geneva 2011. https://apps.who.int/iris/handle/10665/70523.

[23] International Expert C. International Expert Committee report on the role of the A1C assay in the diagnosis of diabetes. Diabetes Care 2009;32:1327–34.

Dimitrios Tsilingiris**
First Department of Propaedeutic Internal Medicine, School of Medicine, National and Kapodistrian University of Athens, Laiko General Hospital, 17 St Thomas Street, 11527, Athens, Greece

Natalia G. Vallianou
First Department of Internal Medicine, Evangelismos General Hospital, 45-47 Ipsilantou Str, 10676, Athens, Greece

Maria Dalamaga*
Department of Biological Chemistry, School of Medicine, National and Kapodistrian University of Athens, 75 Mikras Asias, 11527, Athens, Greece

** Corresponding author. Richard-Kuhn-Str. 1, 69123, Heidelberg, Germany.

* Corresponding author. Clinical Biochemistry, National and Kapodistrian University of Athens, Medical School, Mikras Asias #27, Goudi, 11527, Athens, Greece.
E-mail address: tsilingirisd@gmail.com (D. Tsilingiris).
E-mail address: madalamaga@med.uoa.gr (M. Dalamaga).

4 April 2021
Available online 7 April 2021