Current diagnostic criteria identify risk for type 2 diabetes too late

Bergman, Michael

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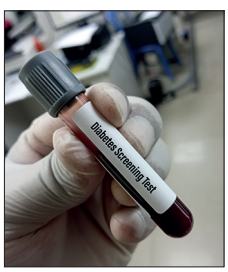
Current diagnostic criteria identify risk for type 2 diabetes too late

The inadequacy of current diagnostic criteria to detect dysglycaemia earlier in the lengthy trajectory to type 2 diabetes could inadvertently be contributing to the burgeoning prevalence of prediabetes and diabetes. This inadequacy originates from several factors. First, criteria for prediabetes are confusing because of the different glucose threshold concentrations recommended by the American Diabetes Association (ADA) and WHO: although the recommended diagnostic criteria for impaired glucose tolerance are the same, those that define impaired fasting glucose are different.[1] Furthermore, ADA (but not WHO due to lack of evidence) recommends measuring HbA_{1c} concentrations for detecting prediabetes.[1] An international consensus is therefore required to resolve these discrepancies.[1] Second, although glucose criteria are absolute, dysglycaemia is generally recognised to occur as a continuous process, and therefore any threshold values will be arbitrary.[2] Third, plasma glucose and HbA_{1c} concentrations are discordant for detecting dysglycaemia, with only a small proportion of the population showing overlapping results. Many clinical conditions can affect HbA_{1c} concentrations (eg, anaemia, genetics, racial or ethnic differences, chronic kidney disease, and haemoglobinopathies), which can result in either overestimation or underestimation of diabetes prevalence.[3] Finally, physiological fasting and 2-h postprandial glucose concentrations are substantially lower than the currently established criteria for defining prediabetes and diabetes, thus leading to increased risk of progressing to type 2 diabetes.[4] For example, fasting plasma glucose concentrations less than 5·6 mmol/L in young men (aged 26–45 years) predicted progression to type 2 diabetes nearly 6 years later.[5]

The Whitehall II Study, which recruited British civil servants without diabetes at baseline, showed that, during a 13-year follow-up, fasting and post-load glucose concentrations initially increased linearly, followed by a rapid increase in concentrations 6 years to 3 years before the onset of type 2 diabetes.[6] Subsequent progression to type 2 diabetes was related to a rapid decline in β-cell function resulting in decreased insulin secretion, attributed to worsening insulin resistance in peripheral tissues. The authors concluded that "people with prediabetes are already on the steep part of the glucose trajectory" and "that prevention would be more effective before this unstable period".[6] Insulin clamp studies support these observations and have found that β-cell function deteriorates incrementally even when glucose concentrations are less than established thresholds for prediabetes, and it progressively worsens with occurrence of prediabetes and type 2 diabetes.[3]

To prevent or delay the onset of type 2 diabetes, the implementation of interventions should occur while high-risk individuals are on the extensive, stable period of the dysglycaemic continuum. Reversal of prediabetes in the Diabetes Prevention Program was most likely to occur if participants regressed to normal glucose tolerance at least once during yearly visits, and it was linked to baseline β-cell function.[7] Regression to normal glucose tolerance occurred only in about a third of individuals during the Diabetes Prevention Program Outcomes Study.[7] Participants regressing to normal glucose tolerance had a 56% decreased risk of progressing to type 2 diabetes and a 22–30% lower prevalence of aggregate microvascular disease related to a reduction in glycaemic exposure.[7] Consequently, microvascular complications could have resulted from extended exposure to non-physiological glucose concentrations before developing prediabetes, as currently defined. However, the benefit of diabetes prevention with regard to major cardiovascular outcomes is less conclusive. Additionally, individuals with prediabetes are at higher risk than individuals without prediabetes, not only for cardiovascular and microvascular disease but also neuropathy, stroke, non-alcoholic fatty liver disease, sleep apnoea, cancer, and dementia. Type 2 diabetes is also associated with similar complications; however, the risk for such complications is lower in individuals with prediabetes than in those with type 2 diabetes.[3] Preservation of β-cell function, early diagnosis, and intensive management are therefore essential to prevent progression of dysglycaemia and restore normal glucose homoeostasis.

Postprandial or post-challenge glucose elevation is generally the first dysfunction in people with



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dysglycaemia. Compared with conventional criteria, a biomarker that can identify high-risk individuals at an earlier timepoint would further substantiate that current criteria for diagnosing prediabetes do so late in the disease process. The 1-h plasma glucose concentration during the oral glucose tolerance test is a more sensitive biomarker than fasting plasma glucose, 2-h plasma glucose, or HbA_{1c} concentrations.[3] 1-h plasma glucose concentration has shown optimal sensitivity and specificity for predicting progression to type 2 diabetes in cross-sectional and longitudinal studies involving diverse populations.[3] 1-h plasma glucose concentrations equal to, or higher than, 8·6 mmol/L, which is used as a threshold for detecting prediabetes, occur in 25–42% of high-risk individuals with normal glucose tolerance defined by current criteria.[3] This threshold value can distinguish individuals at greater risk for progression to type 2 diabetes, retinopathy, cardiovascular disease, and mortality. Biological evidence shows worse metabolic and atherogenic profiles in individuals with elevated 1-h plasma glucose concentrations, which might explain their increased risk for cardiovascular disease.[3]

β-cell function is better preserved in individuals with 1-h plasma glucose concentrations less than 8·6 mmol/L than in those with concentrations equal to, or higher than, 8·6 mmol/L, and it progressively deteriorates with impaired glucose tolerance and type 2 diabetes. Lifestyle intervention should therefore be more beneficial when dysglycaemia is detected at an earlier stage in the trajectory to type 2 diabetes.[3] The STOP Diabetes Study showed that lifestyle intervention and pharmacological therapy were effective in individuals with normal (ie, below current criteria for prediabetes) fasting and 2-h plasma glucose concentrations, but with 1-h plasma glucose concentrations equal to, or higher than, 8·6 mmol/L.[8] Approximately 80% of individuals with impaired glucose tolerance alone and 94% with combined impaired fasting glucose and impaired glucose tolerance have elevated 1-h plasma glucose concentrations and would therefore benefit from diabetes prevention interventions.[3]

The elevated 1-h plasma glucose concentration has also been associated with increased risk for non-alcoholic fatty liver disease and hepatic fibrosis.[9] The 1-h plasma glucose concentration is also sensitive for identifying high-risk children and adolescents. Importantly, a new screening tool needs to be cost-effective from a public-health perspective to be acceptable by payers. A health economic assessment has suggested the cost-effectiveness of using 1-h plasma glucose concentration and subsequent interventions, including lifestyle and metformin, for screening.[10]

Because the 1-h plasma glucose concentration with a threshold of 11·6 mmol/L has increased diagnostic sensitivity and specificity for type 2 diabetes, a 1-h oral glucose tolerance test could detect prediabetes and diabetes earlier.[11] Shortening the duration of the oral glucose tolerance test from 2 h to 1 h could be more practical and acceptable in a clinical setting. In summary, use of the 1-h plasma glucose concentration for screening could achieve the objective of maintaining high-risk individuals on the linear part of the trajectory, thereby delaying or preventing progression to type 2 diabetes.[6]

Because the 1-h oral glucose tolerance test would be impractical for population screening, high-risk individuals (ie, people who have overweight or obesity, are sedentary, or are first-degree relatives of people with diabetes, and people with a history of cardiovascular disease, hypertension, dyslipidaemia, or polycystic ovary syndrome) could initially be screened with a validated questionnaire such as the Finnish Diabetes Risk Score. Individuals younger than 75 years should preferentially be screened because detecting prediabetes in an older population might be less beneficial. Frequency of subsequent testing should be individualised on the basis of risk severity and initial laboratory results. Because of the considerable socioeconomic and personal burden associated with the development of type 2 diabetes, the implementation of a more sensitive strategy for earlier identification of high-risk individuals will be important to decrease the growing prevalence of dysglycaemia and benefit global health.

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Michael Bergman, Martin Buysschaert, Antonio Ceriello, Akhtar Hussain, Viswanathan Mohan, Giorgio Sesti, Jaakko Tuomilehto
michael.bergman@nyulangone.org

Division of Endocrinology, Diabetes and Metabolism, New York University Grossman School of Medicine, New York, NY 10010, USA (MBe); Department of Endocrinology and Diabetology, Université Catholique de Louvain, University Clinic Saint-Luc, Brussels, Belgium (MBu); IRCCS MultiMedica, Milan, Italy (AC); Faculty of Health Sciences, Nord University, Bodø, Norway (AH); Faculty of Medicine, Federal University of Ceará, Fortaleza, Brazil (AH); International Diabetes Federation, Brussels, Belgium (AH); Diabetes in Asia Study Group, Doha, Qatar (AH); Centre for Global Health Research, Diabetic Association of

Bangladesh, Dhaka, Bangladesh (AH); Dr Mohan's Diabetes Specialities Centre and Madras Diabetes Research Foundation, Chennai, India (VM); Department of Clinical and Molecular Medicine, Sapienza University of Rome, Rome, Italy (GS); Public Health Promotion Unit, Finnish Institute for Health and Welfare, Helsinki, Finland (JT); Department of Public Health, University of Helsinki, Helsinki, Finland (JT); Saudi Diabetes Research Group, King Abdulaziz University, Jeddah, Saudi Arabia (JT); Department of International Health, National School of Public Health, Instituto de Salud Carlos III, Madrid, Spain (JT)

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