Counterpoint: Impaired Fasting Glucose: The Case Against the New American Diabetes Association Guidelines

Definitions of diabetes and impaired fasting glucose

The clinical symptoms of type 2 diabetes were described in 1500 BC (1). Until today, diabetes in clinical practice is still often diagnosed when patients present with symptoms. With increasing knowledge of the pathophysiology of the disease, the diagnosis of diabetes was based on the presence of hyperglycemia. Since 1979, internationally accepted definitions and diagnostic cut points for diabetes have been available (Table 1) (2–4). The initial cut points were based on the sharp increase of the prevalence of microvascular disease with increasing glucose. Diagnostic cut points were based on fasting glucose, as well as on glucose concentration 2 h after a 75-g oral glucose tolerance test (OGTT). The OGTT further allowed the identification of a category termed "impaired glucose tolerance" (IGT), which infers a very high risk of diabetes. The OGTT, however, turned out to be problematic in clinical practice, as it is little used. It has become a measure that is mainly used in clinical research. Therefore, in 1997, the American Diabetes Association (ADA) introduced a new definition that no longer required an OGTT (3). The cut point of fasting glucose was lowered with the expectation that most of the subjects with diabetic postload glucose levels would be captured with this lower cut point. In addition, a new category with high risk of diabetes was introduced, termed "impaired fasting glucose" (IFG), again with the expectation that most subjects with IGT would also have IFG.

After the publication of these criteria, a host of epidemiological studies showed a lack of agreement between categories of glucose status based on fasting and postload glucose. Prospective observational studies also showed that IFG and IGT were independent predictors of future diabetes, with cumulative effects (5), and that postload glucose was more strongly associated with the risk of cardiovascular disease (CVD) and mortality (6,7). Therefore, in 1999, when the World Health Organization (WHO) followed the ADA cut point for fasting glucose and the definition of IFG, the use of the OGTT was still recommended (4). For the ADA, new results prompted a reevaluation of the diagnostic criteria, which led to a change in the definition of IFG in 2003 (8). The new lower cut point for the definition of IFG was "evidence based" and selected as the level of fasting glucose with the highest sensitivity and specificity to predict incident diabetes in four population studies. An important argument was that by lowering the IFG cut point, more subjects with IGT would also be identified.

The ability to predict diabetes is a very important criterium for the definition of IFG, but should it be the only one (9)? Below, we review the consequences of the new IFG criteria with respect to IFG prevalence, risk of diabetes, risk of CVD, and, finally, public health implications.

The prevalence of IFG

In the U.S., in the NHANES (National Health and Nutrition Examination Survey) study, the prevalence of IFG increased about threefold from 7% with fasting glucose 6.1–6.9 mmol/l to 24% with fasting glucose 5.6–6.9 mmol/l. This was similar for all ethnic groups, but the increase was more pronounced in the younger age-group of 20–50 years (almost 5-fold) than in those ≥65 years (1.5-fold increase) (9). In the Hoorn study, a Dutch population-based study of 2,484 men and women aged 50–75 years, 12% had a fasting glucose value of 6.1–7.0 mmol/l. Lowering the cut point to 5.6 mmol/l increased the prevalence of IFG about threefold to 35% (6). A threefold increase in the prevalence of IFG by the new criteria, from 10–15% to 30–45%, was also observed in the DETECT-2 project (10). This project includes large studies from Denmark (Inter99, 6,265 subjects), France (Paris Prospective, 7,034 subjects), China (Qingdao, 1,808 subjects), India (NUDS [National Study on Urban Prevalence of Diabetes], 10,039 subjects), and the U.S. (NHANES, 3,517 subjects). The percentage of people with IFG who also had IGT decreased by >30% in the Danish, French, and Indian populations, with a 17 and 18% decrease in the Chinese and American populations, respectively. Also in a study among 4,723 subjects in the 1998 National Health Survey in Singapore, the prevalence of IFG increased from 10 to 32%. The percentage of subjects with IGT was 39% in the category with fasting glucose 6.1–6.9 mmol/l, 20% in those with fasting glucose 5.6–6.0 mmol/l, and 8% in those with fasting glucose <5.6 mmol/l. Of all subjects with IGT, 36% had normal fasting glucose (<5.6 mmol/l) (11). In the DESIR (Data from an Epidemiological Study on the Insulin Resistance syndrome) study in France, the percentage with IFG increased from 13 to 40% in the 2,176 men and from 4 to 15% in the 2,267 women (12). In 1,285 employees of the Italian Telephone Company, the percentage with IFG increased from 3 to 10% (13).

Thus, with the new criteria, worldwide, ~30–40% of the adult population is considered to have IFG, in contrast to 7–10% with the old criteria.

IFG and risk of diabetes

The higher prevalence of IFG with the new criteria is accompanied with a much lower risk of future diabetes. In the Hoorn study, the 6-year incidence of diabetes, as determined by a follow-up OGTT (both fasting and postload glucose used), was 5% in those with fasting plasma glucose (FPG) <5.6 mmol/l, 14% in the category 5.6–6.0 mmol/l, and 44% in the category 6.1–6.9 mmol/l (unpublished data). In the DESIR study, the threefold higher prevalence was accompanied by a sevenfold reduction in diabetes risk (12). The incidence per 1,000 person-years for the categories of <5.6, 5.6–6.0, and 6.1–6.9 mmol/l were 1.8, 5.7, and 43.2% in men and 0.7, 6.2, and 54.7% in women, respectively. Also, in the Singapore Impaired Glucose Tolerance Follow-up Study, among 596 subjects, with oversampling for baseline IGT, the 8-year incidence of diabetes was 2, 22, and 55%

Table 1—*Diagnostic criteria for diabetes and impaired glucose regulation, IFG, and IGT*

	NDDG 1979/WHO 1980 and 1985	ADA 1997/WHO 1999	ADA 2003
FPG			
Diabetes	≥140/≥7.8	≥126/≥7.0	≥126/≥7.0
IFG		110–125/6.1–6.9	100–125/5.6–6.9
2-h post–75-g OGTT plasma glucose		Not recommended by ADA	
Diabetes	≥200/≥11.1	≥200/≥11.1	
IGT	140–199/7.8–11.1	140–199/7.8–11.1	

Data are in mg/dl / mmol/l. NDDG, National Diabetes Data Group.

for the categories <5.6, 5.6–6.0, and 6.1–6.9 mmol/l, respectively (11).

Besides increased FPG, other risk factors contribute to diabetes risk. The presence of the metabolic syndrome, defined as three or more of abdominal obesity, high blood pressure, high triglycerides, low HDL cholesterol, or IFG, with a prevalence of ~20%, is associated with a threefold risk of diabetes (14). In the ARIC (Atherosclerosis Risk in Communities) study, risk scores to predict incident diabetes were developed (15). Selection of the 20% with the highest risk score based on age, ethnicity, parental history of diabetes, systolic blood pressure, waist circumference, height, and FPG attained a sensitivity of 51% and a specificity of 86%.

IFG and risk of all-cause and CVD mortality

After the introduction of the category IFG by the ADA in 1997, the Hoorn study showed similar reproducibility of categorizing subjects for IGT and IFG (16), and subjects with fasting glucose of 6.1–6.9 mmol/l were at increased risk of mortality (7). However, subjects with fasting glucose 5.6–6.0 mmol/l actually had a lower risk than those with lower fasting glucose levels (7). This U-shaped association between fasting glucose level and all-cause and CVD mortality was also observed in the Paris Prospective Study (17) and other prospective European population studies, which were combined in the DECODE study (18). In the U.S., in 2,673 postmenopausal women with coronary artery disease, the 7-year risk of coronary heart disease relative to women with fasting glucose <5.6 mmol/l was lower in women with fasting glucose 5.6–6.0 mmol/l and higher in women with glucose 6.1–6.9 mmol/l (19). This U- or J-shaped relationship was also observed in Taiwan for 36,386 subjects aged 40–69 years (20). The BLSA (Baltimore Longitudinal Study of Aging), which studied 1,236 men from the general U.S. population, also did not find increased risks in men with fasting glucose 5.6–6.0 mmol/l (21).

Evidence is accumulating that in the population with FPG 5.6–6.9 mmol/l (the 30% of the population with highest risk of diabetes), only the upper 10%, with fasting glucose 6.1–6.9 mmol/l (the previous IFG criteria), also have increased risk of all-cause and cardiovascular mortality. Although type 2 diabetes and CVD have several risk factors in common, there are differences in the pathophysiology and consequently in the optimal cut points of risk factors in risk stratification.

In addition, it is now clear that IFG and IGT reflect different physiological processes (22) that occur in different subjects and that differ with respect to their association with CVD (6,7).

Public health implications

In summary, the new criteria for IFG have resulted in labeling a third of the general population at high risk of diabetes. The absolute risk of diabetes in this category is still relatively low, so the number of subjects who are labeled "high risk" is dramatically increasing, but the majority will never develop diabetes. In addition, in contrast to subjects with IGT and subjects with fasting glucose 6.1–6.9 mmol/l, subjects with fasting glucose 5.6–6.0 mmol/l do not have an increased risk of CVD. The ADA, in its position statement, refers to patients with IFG and/or IGT as having "pre-diabetes" (23). This leads to confusion, because the term pre-diabetes is also used to indicate a category of subjects with very high risk of both CVD and diabetes; this group should be targeted for primary prevention and intensive treatment of risk factors. This is no longer true with the new criteria.

JACQUELINE M. DEKKER, PHD[1]
BEVERLEY BALKAU, PHD[2]

From the [1]Institute for Research in Extramural Medicine, VU University Medical Center, Amsterdam, the Netherlands; and [2]INSERM U258, Villejuif, France.

Address correspondence to Jacqueline M. Dekker, Institute for Research in Extramural Medicine, VU University Medical Center, Van der Boechorststraat 7, 1081 BT Amsterdam, Netherlands. E-mail: jm.dekker@vumc.nl.

DOI: 10.2337/dc05-2220

References

1. MacFarlane IA, Bliss M, Jackson JGL, Williams G: The history of diabetes melllitus. In *Textbook of Diabetes*. 2nd ed. Pickup J, Willams G, Eds. London, Blackwell Science, 1997
2. World Health Organization: *Diabetes Mellitus: Report of a WHO Study Group*. Geneva, World Health Org., 1985 (Tech. Rep. Ser., no 727)
3. The Expert Committee on the Diagnosis and Classification of Diabetes Mellitus: Report of the Expert Committee on the Diagnosis and Classification of Diabetes Mellitus. *Diabetes Care* 20:1183–1197, 1997
4. World Health Organization: *Definition, Diagnosis, and Classification of Diabetes Mellitus and Its Complications: Report of a WHO consultation. Part 1: Diagnosis and Classification of Diabetes Mellitus*. Geneva, World Health Org., 1999 (WHO/NCD/NCS/99.2)
5. de Vegt F, Dekker JM, Jager A, Hienkens E, Kostense PJ, Stehouwer CDA, Nijpels G, Bouter LM, Heine RJ: Relation of impaired fasting and postload glucose with incident type 2 diabetes in a Dutch population: the Hoorn study. *JAMA* 285: 2109–2113, 2001
6. de Vegt F, Dekker JM, Ruhé HG, Stehouwer CDA, Nijpels G, Bouter LM, Heine RJ: Hyperglycaemia is associated with all-cause and cardiovascular mortality in the Hoorn population: the Hoorn Study. *Diabetologia* 42:926–931, 1999

7. The DECODE Study Group, the European Diabetes Epidemiology Group: Glucose tolerance and cardiovascular mortality: comparison of fasting and 2-hour diagnostic criteria. *Arch Intern Med* 161:397–405, 2001
8. The Expert Committee on the Diagnosis and Classification of Diabetes Mellitus: Follow-up report on the diagnosis of diabetes mellitus. *Diabetes Care* 26:3160–3167, 2003
9. Davidson MB, Landsman PB, Alexander CM: Lowering the criterion for impaired fasting glucose will not provide clinical benefit (Editorial). *Diabetes Care* 26: 3329–3330, 2003
10. Borch-Johnson K, Colaiuri S, Balkau B, Glümer C, Carstensen B, Ramachandran A, Dong Y, Gao W: Creating a pandemic of prediabetes: the proposed new diagnostic criteria for impaired fasting glycemia. *Diabetologia* 47:1396–1402, 2004
11. Tai ES, Goh SY, Lee JJM, Wong MS, Heng D, Hughes K, Chew SK, Cutter J, Chew W, Gu K, Chia KS, Tan CE: Lowering the criterion for impaired fasting glucose: impact on disease prevalence and associated risk of diabetes and ischemic heart disease. *Diabetes Care* 27:1728–1734, 2004
12. Balkau B, Hillier T, Vierron E, D'Hour A, Lépinay P, Royer B, Born C: Comment to: Borch-Johnsen K, Colagiuri S, Balkau B, et al. (2004): Creating a pandemic of prediabetes: the proposed new diagnostic criteria for impaired fasting glycaemia. *Diabetologia* 48:801–802, 2005
13. Vaccaro O, Riccardi G: Changing the definition of impaired fasting glucose: impact on the classification of individuals and risk definition. *Diabetes Care* 28:1786–1788, 2005
14. Ford E: Risks for all-cause mortality, cardiovascular disease, and diabetes associated with the metabolic syndrome: summary of the evidence. *Diabetes Care* 28:1769–1798, 2005
15. Schmidt MI, Duncan BB, Bang H, Pankow JS, Ballantyne CM, Golden SH, Folsom AR, Chambless LE, the ARIC Investigators: Identifying individuals at high risk for diabetes: the Atherosclerosis Risk in Communities study. *Diabetes Care* 28:2013–2018, 2005
16. Vegt F de, Dekker JM, Stehouwer CDA, Nijpels G, Bouter LM, Heine RJ: Similar 9-year mortality risks and reproducibility for the World Health Organization and American Diabetes Association glucose tolerance categories: the Hoorn Study. *Diabetes Care* 23:40–44, 2000
17. Balkau B, Bertrais S, Ducimetiere P, Eschwege E: Is there a glycemic threshold for mortality risk? *Diabetes Care* 22:696–699, 1999
18. The DECODE Study Group, the European Diabetes Epidemiology Group: Is the current definition for diabetes relevant to mortality risk from all causes and cardiovascular and no cardiovascular diseases? *Diabetes Care* 26:688–696, 2003
19. Kanaya AM, Herrington D, Vittinghoff E, Lin F, Bittner V, Cauley JA, Hulley S, Barrett-Connor E: Impaired fasting glucose and cardiovascular outcomes in postmenopausal women with coronary artery disease. *Ann Intern Med* 142:813–820, 2005
20. Wen CP, Cheng TYD, Tsai SP, Hsu HL, Wang SL: Increased mortality risks of pre-diabetes (impaired fasting glucose) in Taiwan. *Diabetes Care* 28:2756–2761, 2005
21. Sorkin JD, Muller DC, Fleg JL, Andres R: The relation of the fasting and 2-h postchallenge plasma glucose concentrations to mortality: data from the Baltimore Longitudinal Study of Aging with a critical review of the literature. *Diabetes Care* 28: 2626–2632, 2005
22. Ferrannini E, Gastaldelli A, Miyazaki Y, Masuda M, Mari A, DeFronzo RA: B-cell function in subjects spanning the range from normal glucose tolerance to overt diabetes: a new analysis. *J Clin Endocrinol Metab* 90:493–500, 2005
23. American Diabetes Association: Diagnosis and classification of diabetes mellitus (Position Statement). *Diabetes Care* 28 (Suppl. 1):S37–S42, 2005