Cardiovascular disease in older adults with glucose disorders: comparison of American Diabetes Association criteria for diabetes mellitus with WHO criteria

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Summary

Background The new fasting American Diabetes Association (ADA) criteria for the diagnosis of diabetes mellitus rely mainly on fasting blood glucose concentrations and use a lower cut-off value for diagnosis than the WHO criteria. We aimed to assess the sensitivity of these criteria for the detection of cardiovascular disease, the main complication of diabetes mellitus in the elderly.

Methods We did a cross-sectional and prospective analysis of 4515 participants of the Cardiovascular Health Study, an 8-year longitudinal study designed to identify factors related to the onset and course of cardiovascular disease in adults aged at least 65 years. We calculated the prevalence and incidence of cardiovascular disease for the ADA and WHO criteria.

Findings There was a higher prevalence of cardiovascular disease among individuals with impaired glucose or newly diagnosed diabetes by both criteria than among those with normal glucose concentrations. However, because fewer individuals had abnormal glucose states by the fasting ADA criteria (22·3%) than by the WHO criteria (46·8%), the number of cases of cardiovascular disease attributable to abnormal glucose states was a third of that attributable by the WHO criteria (53 vs 159 cases per 10 000). For the two sets of criteria, the relative risk for incident cardiovascular disease (mean follow-up 5·9 years) was higher in individuals with impaired glucose and newly diagnosed diabetes than in those with normal glucose. Individuals classified as normal by the fasting ADA criteria had a higher absolute number of incident events (455 of 581 events) than those classified as normal by the WHO criteria (269 of 581 events). Fasting ADA criteria were therefore less sensitive than the WHO criteria for predicting cardiovascular disease among individuals with abnormal glucose (sensitivity, 28% *vs* 54%).

Interpretation The new fasting ADA criteria seem to be less predictive than the WHO criteria for the burden of cardiovascular disease associated with abnormal glucose in the elderly.

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Introduction

In 1997, the American Diabetes Association (ADA) published criteria for the diagnosis and classification of diabetes mellitus and related glucose disturbances.[1] In the absence of weight loss, polyuria, polydipsia, and a blood glucose concentration 2 h after load of at least 11·1 mmol/L, these new criteria rely primarily on fasting glucose values. The advantage of the ADA criteria is that they do not require oral glucose tolerance testing with 2 h glucose measurements, as set forth by the WHO criteria.[2] By simplifying the diagnosis of diabetes mellitus, ADA hoped that the diagnosis of glucose metabolic disturbances would be simpler and less of a burden to patients, more readily accepted by the medical community, and would lead to earlier detection and treatment of individuals with diabetes mellitus.

The fasting ADA criteria establish a fasting glucose concentration of at least 7·0 mmol/L for the diagnosis of diabetes mellitus, which is lower than the corresponding WHO criteria of at least 7·8 mmol/L. This lower cut-off point was chosen because the microvascular eye and kidney diseases that are unique to diabetes mellitus begin to become more prevalent at this concentration. The fasting ADA criteria also define a new class of glucose disturbance called impaired fasting glucose (fasting glucose 6·1–6·9 mmol/L), which differs from the WHO category of impaired glucose tolerance (fasting glucose <7·8 mmol/L and 2 h glucose ⩾7·8 mmol/L and <11·1 mmol/L).

We previously compared the amount of agreement of the fasting ADA and the WHO criteria in the Cardiovascular Health Study,[3] a population-based longitudinal study of adults aged 65 years and older, which was designed to identify factors related to the onset and course of coronary heart disease, stroke, and cardiovascular death (cardiovascular disease). We found only a modest correlation between the two sets of criteria. Among 4515 participants with no history of diabetes mellitus, the fasting ADA criteria classified 3509 (77·7%) as normoglycaemic and 1006 (22·3%) as abnormal (14·6% impaired fasting glucose and 7·7% newly diagnosed diabetes mellitus). The WHO criteria classified 2401 (53·2%) as normoglycaemic, and 2114 (46·8%) as abnormal (32·1% impaired glucose tolerance and 14·8% newly diagnosed diabetes mellitus). More importantly, 1309 (37·3%) of 3509 individuals defined as normoglycaemic by the fasting ADA criteria had abnormal glucose concentrations by the WHO criteria

(31·4% impaired glucose tolerance and 5·9% newly diagnosed diabetes mellitus). This discrepancy occurred because of the high proportion of participants who had fasting glucose concentrations less than 6·1 mmol/L but 2 h glucose concentrations of at least 7·8 mmol/L. Age was more strongly associated with 2 h glucose concentrations than with fasting glucose concentrations. Other studies have noted similar degrees of discrepancy between the fasting ADA and WHO criteria.[4,5]

These findings raise the question of which criteria are more appropriate for the identification of glucose disturbances in older people. Since one of the purposes of diagnostic criteria is to improve the ability to detect risk for disease complications, one way to answer this question is to assess the ability of the two criteria to predict the prevalence and incidence of cardiovascular disease, the most common complication of glucose abnormalities in the elderly. We analysed the Cardiovascular Health Study dataset to assess the prevalence and incidence of cardiovascular disease by the ADA and WHO diagnostic criteria.

Patients and methods

Recruitment

Details of the recruitment and methods of the Cardiovascular Health Study have been published.[6] Briefly, a random sample of patients from the Health Care Finance Administration Medicare eligibility lists in four US communities were invited to participate. Potential participants were excluded if they were institutionalised, wheelchair-bound in the home, or had severe illnesses that were expected to lead to early death. Patients were recruited in two phases. The first phase took place from June, 1989, to May, 1990. 5201 eligible men and women (4926 white [94·7%], 244 black [4·7%], 31 other [0·6%]) aged 65 years and older agreed to participate. In 1992–93, the second phase of the study was undertaken to provide additional representation of black people. 687 participants (672 black [97·8%], 15 other [2·2%]) were recruited in a similar way to the first phase.

Study design

After an overnight fast, venepuncture was done at the start of the clinic visit. After initial blood samples were collected, we did an oral glucose tolerance test by 75 g glucose load (consumed within 10 min) in patients with no history of diabetes mellitus requiring insulin or oral hypoglycaemic agents. An additional venepuncture for measurement of glucose was done 2 h later. Plasma and serum were frozen at –70°C and shipped to the Cardiovascular Health Study central laboratory (University of Vermont, Burlington, VT, USA). Glucose concentrations were measured on a Kodak Ektachem 700 Analyzer (Ektachem Test Methodologies, Eastman Kodak, Rochester, NY, USA). All fasting and 2 h glucose samples were assayed within 30 days. Average monthly coefficient of variation was 0·93%.[7] During the clinic visit, participants were asked questions about their previous health, including whether they had a history of myocardial infarction or stroke. Current medication use, including insulin and oral hypoglycaemic agents, was also ascertained.

Clinical coronary heart disease was defined as a baseline history of myocardial infarction, confirmed by medical-record review, or myocardial infarction during follow-up. Clinical cerebrovascular disease was defined as a baseline history of stroke, confirmed by medical-record review, or stroke during follow-up. Incident coronary heart disease or stroke were adjudicated by committee by use of previously published definitions.[8,9]

Participants' glycaemic categories were determined at study entry based on the results of fasting blood glucose, 2 h glucose during oral glucose tolerance test, or the use of insulin or oral hypoglyaemic agents. Self-report of diabetes was not used to define diabetes mellitus. Only individuals who had not eaten within 9 h of blood samples being taken, who had fasting and 2 h glucose measurements, and who were not being treated for diabetes were analysed. 390 (7·5%) participants who were using insulin or oral hypoglycaemic agents and 296 participants (5·7%) with missing fasting or 2 h glucose concentrations from the original cohort were therefore excluded from the first-phase cohort. The remaining 4515 (86·8%) participants were included in the analysis. In the second-phase cohort, 145 (21·6%) black participants had used insulin or oral hypoglycaemic agents. An additional 265 (39·4%) participants had missing fasting or 2 h glucose concentrations. The remaining 262 (39·0%) participants were included in the analysis. Because of these small numbers the latter cohort was not included in this study.

Statistical analysis

We calculated prevalence of coronary heart disease and cerebrovascular disease for the two diagnostic criteria. Disease prevalence was computed for each classification of glycaemia according to the ADA and WHO criteria. We calculated attributable risks to assess effects of exposures. We then calculated disease-free survival from coronary heart disease, cerebrovascular disease, and cardiovascular death, and used Cox's proportional hazards models to estimate the relative risks for these events by each criteria. Fasting ADA and WHO classifications were entered as categorical covariates in two different models. For each model, the normoglycaemic group was the reference group. Models were adjusted for sex, age, ethnic group, and cardiovascular disease risk factors. Sex and ethnic group were included as dichotomous variables, and age was included as a continuous variable. Smoking status was classified as never, former, or current; body-mass index as lowest quintile, second to fourth quintile, and upper quintile; and LDL cholesterol as first and second quintile versus the upper three quintiles. Hypertension was defined as use of hypertensive medications or blood pressure of more than 160/96 mm Hg. All statistical calculations were done with SPSS for Windows, version8.0.

Results

The mean baseline age of the original cohort was 73 years (SD 5·6). There were 2619 (58%) women and 1896 (42%) men; 4303 (95·3%) of the participants were white. The mean fasting glucose was 5·8 mmol/L (SD 1·3) and the median was 5·6 mmol/L. The mean 2 h glucose was 8·2 mmol/L (3·2) and the median was 7·5 mmol/L.

The prevalence of coronary heart disease and cerebrovascular disease by the two diagnostic criteria was similar (table 1). By the WHO criteria, 12·7% of participants classified as having impaired glucose tolerance and 15·5% as having newly diagnosed diabetes mellitus had cardiovascular disease. By the fasting ADA criteria, 11·4% with impaired fasting glucose and 17·8% with newly diagnosed diabetes mellitus had cardiovascular disease.

We calculated the prevalence of cardiovascular disease attributable to abnormal glucose concentrations to adjust for the fact that there were about twice as many participants with impaired glucose and newly diagnosed diabetes

	History of myocardial infarction or stroke		Total
	No	Yes	
WHO*			
Normal	2157 (89·8%)	244 (10·2%)	2401
Impaired glucose tolerance	1264 (87·3%)	184 (12·7%)	1448
New diabetes mellitus	563 (84·5%)	103 (15·5%)	666
Total	3984 (88·2%)	531 (11·8%)	4515
Fasting ADA†			
Normal	3115 (88·8%)	394 (11·2%)	3509
Impaired fasting glucose	582 (88·6%)	75 (11·4%)	657
New diabetes mellitus	287 (82·2%)	62 (17·8%)	349
Total	3984 (88·2%)	531 (11·8%)	4515

*p<0·001, χ^2 test for trend. †p=0·002, χ^2 test for trend.

Table 1: **Baseline prevalence of history of myocardial infarction or stroke according to WHO and fasting ADA criteria**

	n	Relative risk (95% CI)	
		Adjusted for sex, age, and ethnic group	Adjusted for sex, age, ethnic group and cardiovascular disease risk factors
Relative to normal of each diagnostic criteria			
WHO			
Normal	2157	1·00	1·00
Impaired glucose tolerance	1264	1·23 (1·02–1·48)	1·22 (1·01–1·48)
New diabetes mellitus	563	1·65 (1·33–2·05)	1·55 (1·23–1·95)
Fasting ADA			
Normal	3115	1·00	1·00
Impaired fasting glucose	582	1·37 (1·10–1·70)	1·28 (1·02–1·61)
New diabetes mellitus	287	1·54 (1·18–2·03)	1·46 (1·09–1·94)
Relative to common standard*			
WHO			
Common normal	1973	1·00	1·00
Normal	184	1·14 (0·77–1·69)	1·09 (0·73–1·65)
Impaired glucose tolerance	1264	1·24 (1·03–1·50)	1·23 (1·01–1·98)
New diabetes mellitus	563	1·67 (1·34–2·09)	1·56 (1·23–1·98)
Fasting ADA			
Common normal	1973	1·00	1·00
Normal	1142	1·21 (1·00–1·47)	1·20 (0·99–1·47)
Impaired fasting glucose	582	1·48 (1·17–1·86)	1·39 (1·09–1·77)
New diabetes mellitus	287	1·67 (1·26–2·21)	1·58 (1·17–2·13)

*Fasting glucose <6·1 mmol/L and 2 h post-load glucose <7·8 mmol/L.

Table 2: **Relative risk for coronary artery disease, stroke, or cardiovascular death (excluding baseline cardiovascular disease)**

mellitus by the WHO criteria as there were by the fasting ADA criteria. By the WHO criteria, 2114 (46·8%) individuals had abnormal glucose concentrations (32·1% impaired glucose tolerance, 14·8% new diabetes mellitus). Of these 2114 participants, 13·6% (184 and 103, respectively) had cardiovascular disease. Among individuals classified as normal by the WHO criteria, there was a 10·2% prevalence (244 of 2401) of cardiovascular disease. The number of individuals with cardiovascular disease attributable to abnormal glucose concentrations was therefore 159 cases per 10 000 (46·8%×[13·6%−10·2%]). By the fasting ADA criteria, 1006 (22·3%) had abnormal glucose concentrations (14·6% impaired fasting glucose, 7·7% new diabetes mellitus). Of these participants, 13·6% (75 and 62, respectively) had cardiovascular disease. Among individuals classified as normal by the ADA criteria, there was an 11·2% prevalence (394 of 3509) of cardiovascular disease. The number of cases of cardiovascular disease attributable to abnormal glucose concentrations by the fasting ADA criteria was therefore 53 cases per 10 000 (22·3%×[13·6%−11·2]).

Among the 3984 individuals without baseline coronary heart disease or cerebrovascular disease, there were 581 new cardiovascular-disease events or deaths during a mean of 5·9 years of follow-up (median 6·4): 245 coronary heart disease, 221 cerebrovascular disease, 16 coronary heart disease and cerebrovascular disease, and 99 deaths.

Relative risks associated with abnormal glucose concentrations compared with the respective normal category of each criteria were estimated (table 2). The WHO and fasting ADA criteria showed that individuals with impaired glucose and newly diagnosed diabetes mellitus were at increasingly greater risk of cardiovascular disease events than those classified as normal. Adjustment for cardiovascular-disease risk factors yielded similar, although lower, estimates.

To directly compare the two criteria, we calculated a second set of Cox's models using a common reference category (table 2). This common reference group included individuals who were classified normal by WHO and fasting ADA criteria (fasting glucose <6·1 mmol/L and 2 h glucose <7·8 mmol/L). Thus, for this analysis, each criteria had two normal categories: those classified as normal by both criteria, and those classified as normal by one criteria but not by the other. The fasting ADA criteria identified a higher degree of risk for patients with impaired glucose than did the WHO criteria. The degree of risk was similar for individuals with newly diagnosed diabetes mellitus. However, individuals defined as normal by only the fasting ADA criteria were at higher risk than those defined as normal by only the WHO criteria. Individuals classified as normal by the ADA criteria had a relative risk similar to that of individuals with impaired glucose tolerance by the WHO criteria. Analysis of the 209 ADA normal participants who had newly diagnosed diabetes mellitus by the WHO criteria showed an adjusted relative risk for cardiovascular disease of 1·35 (95% CI 0·93–1·96).

Of 581 participants who developed cardiovascular-disease events or died of cardiovascular disease during follow-up, 196 (34%) had impaired glucose tolerance and 116 (20%) had new diabetes mellitus by the WHO criteria (54% sensitivity, 57% specificity; table 3) and 103 (18%) had impaired fasting glucose and 60 (10%) had new diabetes mellitus by the fasting ADA criteria (28% sensitivity, 79% specificity). Thus, more participants with incident cardiovascular disease were classified as having abnormal glucose concentrations by the WHO criteria than by the fasting ADA criteria.

To assess the difference between the two criteria to detect incident events, diabetes-attributable cardiovascular disease that was missed by each diagnostic criteria was calculated. The incidence of cardiovascular disease events and death was similar among individuals with new diabetes mellitus by each criteria alone (21%) and differed from the incidence of events in individuals with normal and impaired glucose by either criteria (14%; 465 of 3421 by WHO, 521 of 3697 by ADA; table 3). The proportion of cardiovascular disease risk attributable to new diabetes mellitus is therefore 7%. If we assume the total new diabetes mellitus group (616 individuals: 563 by WHO criteria, including 234 by ADA criteria, plus 15 and 38 who are normal and have impaired glucose tolerance, respectively, by WHO criteria) with 128 incident events (116 by WHO criteria, and three and nine who are normal and have impaired glucose tolerance, respectively, by WHO criteria) to be the true exposure group, then the fasting ADA criteria missed a diagnosis of diabetes mellitus in 329 (53%) individuals. Of the 68 incident events among these individuals, 4·8 could be attributed to new diabetes mellitus. The WHO criteria did not identify 53 (9%) participants at greater risk, and of the

WHO criteria	ADA criteria (incident cases/number at risk [%])			
	Normal	Impaired fasting glucose	Newly diagnosed diabetes	Total
Normal	241/1973 (12%)	25/169 (15%)	3/15 (20%)	269/2157 (12%)
Impaired glucose tolerance	145/959 (15%)	42/267 (16%)	9/38 (24%)	196/1264 (16%)
Newly diagnosed diabetes	32/183 (17%)	36/146 (25%)	48/234 (21%)	116/563 (21%)
Total	418/3115 (13%)	103/582 (18%)	60/287 (21%)	581/3984 (15%)

Table 3: **Incidence of myocardial infarction, stroke, or cardiovascular death**

12 events in this group, 0·8 could be attributed to new diabetes mellitus.

Discussion

We found that WHO and ADA criteria estimated similar prevalence rates of cardiovascular disease. However, because the fasting ADA criteria defined fewer individuals as having abnormal glucose concentrations than did the WHO criteria, the prevalence of cardiovascular disease attributable to glucose abnormalities was much lower by the fasting ADA criteria.

Likewise, for incident disease, we found that the risk of cardiovascular disease for individuals with abnormal glucose concentrations compared with normal concentrations for each criteria was similar. However, when comparing the two criteria directly with each other, we found that those who were classified normal by the fasting ADA criteria were at higher risk of cardiovascular-disease events than those who were classified as normal by the WHO criteria. Therefore, fewer cardiovascular-disease events and deaths occurred among those with abnormal glucose states by the fasting ADA criteria than by the WHO criteria. The fasting ADA criteria were therefore less sensitive than the WHO criteria.

If the purpose of screening for diabetes mellitus is to identify the maximum number of people at risk of cardiovascular disease, and there is an effective treatment to prevent cardiovascular-disease events or death when glucose is slightly raised, then it would seem that the WHO criteria are superior to the fasting ADA criteria. The UK Prospective Diabetes Study of newly diagnosed individuals with diabetes[10] suggests that keeping glucose concentrations low at an early stage of hyperglycaemia is important in the prevention of cardiovascular disease. Likewise, early recognition of abnormal glucose concentrations may alert the physician to more aggressively manage comorbidities such as hyperlipidaemia, obesity, and hypertension. Treatment strategies for these disorders vary and depend on whether glucose abnormalities are present.[11]

Two points should be born in mind. First, our study did not assess the sensitivity or specificity of fasting and 2 h postprandial glucose concentrations for detecting cardiovascular disease events or death; we attempted only to compare two diagnostic criteria. Second, the ADA and WHO criteria are not mutually exclusive. The ADA criteria, for example, do not negate impaired glucose tolerance if a 2 h oral glucose tolerance test is done, although fasting glucose is deemed the preferred method for diagnosis.

Several potential limitations of this study should be noted. First, we used only one baseline glucose measurement to classify individuals into glucose categories. Over time, many individuals who were normal by either criteria probably developed abnormal glucose concentration. Although these factors may influence the results, there is little reason to believe that change in glucose status would have occurred more often with one set of criteria than with the other. Second, we chose only three well-defined endpoints to define cardiovascular disease: coronary heart disease, cerebrovascular disease, and death. We did not use less well-defined cardiovascular disease entities, such as angina pectoris, heart failure, coronary-artery bypass surgery, or transient ischaemic attack, because hard endpoints are most often assessed in clinical practice. Finally, our analysis was confined to older adults and the results cannot be extrapolated to younger populations.

Our results show that the fasting ADA criteria seem to be less predictive than the WHO criteria of the burden of cardiovascular disease that is associated with glucose disorders in the elderly, which agrees with the results of Barrett-Connor and Ferrara.[12] Glucose abnormalities have their highest prevalence and their greatest impact on population health in the elderly. The implication of our findings is to question the advisability of the use of the fasting ADA criteria for the diagnosis of glucose disorders in the elderly.[13]

Contributors

Joshua I Barzilay contributed to the formulation, analysis, and writing of the paper. Charles F Spiekerman contributed to the analysis and formulation of the paper. Patricia W Wahl contributed to the design and conduct of Cardiovascular Health Study, as well as to the initial analysis of the paper. Lewis H Kuller contributed to the design and conduct of Cardiovascular Health Study, and the analysis and writing of the paper. Mary Cushman participated in the design and laboratory components of the Cardiovascular Health Study, and assisted in the analysis, interpretation, and writing of the paper. Curt D Furberg contributed to the design and conduct of the Cardiovascular Health Study, and participated in the interpretation and writing of the paper. Adrian Dobs and Joseph F Polak contributed to the writing of the paper. Peter J Savage contributed to the design and conduct of Cardiovascular Health Study, and the analysis and writing of the paper.

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