Reproducibility of the Diagnosis of Diabetes Over a 30-Month Follow-Up

The Paris Prospective Study

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OBJECTIVE — To describe the change in diabetic status over 30 months.

RESEARCH DESIGN AND METHODS — Cohort study of 5,400 Caucasian men from the Paris Prospective Study, aged 44–55 years, who were not known as having diabetes at baseline. Oral glucose tolerance tests were performed at baseline and after 30 months.

RESULTS — At baseline, diabetes was diagnosed in 2.9% of the men by fasting plasma glucose (FPG) ≥7.0 mmol/l and in 0.9% by isolated postchallenge hyperglycemia (IPH) (FPG <7.0 mmol/l and 2-h plasma glucose concentration ≥11.1 mmol/l), i.e., one in four of all men with newly diagnosed diabetes. Thirty months later, 42% of the men with diabetes diagnosed by FPG reverted to nondiabetic status, compared with 72% of those with diabetes diagnosed by IPH ($P <$ 0.0001). For the men with diabetes diagnosed by FPG at baseline, diabetes had been diagnosed by a physician at 30 months in 11.5%, in contrast to only 3.9% of those with diabetes diagnosed by IPH ($P < 0.05$). For the 51 men with diabetes diagnosed by IPH at baseline, those who reverted to nondiabetic status had a lower frequency of family history of diabetes ($P < 0.1$), a higher mean corpuscular volume ($P < 0.08$), and a significantly higher total cholesterol concentration ($P < 0.006$) at baseline; in contrast, for the 156 men with diabetes diagnosed by FPG at baseline, the men who reverted to nondiabetic status and those who remained diabetic had similar characteristics.

CONCLUSIONS — In this epidemiological study, diabetes diagnosed by one FPG concentration was more stable than diabetes diagnosed by one IPH; in clinical practice, the diagnosis of diabetes requires confirmation of the hyperglycemia.

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The biological variability of both fasting and 2-h glucose concentrations has been documented, and the various coefficients used to evaluate this variability have shown that the 2-h glucose concentration is more variable than the fasting concentration (1–3). We have already commented on the reproducibility of the diabetic status in the Paris Prospective Study (4) during this 30-month period. When diabetes was defined on the basis of the previous World Health Organization (WHO) definition, fasting plasma glucose (FPG) ≥7.8 mmol/l and/or 2-h glucose ≥11.1 mmol/l (5), only 43% of the men were still considered diabetic, whereas 29% were considered to have impaired glucose tolerance (IGT), and the remaining 28% of the men were considered nondiabetic.

With the current recommendations for screening and diagnosing diabetes using an FPG concentration ≥7.0 mmol/l (6,7), subjects in whom diabetes had been diagnosed by isolated postchallenge hyperglycemia (IPH) (IPH: FPG <7.0 mmol/l and 2-h glucose ≥11.1 mmol/l) will no longer be screened. We evaluated whether diabetes diagnosed by FPG ≥7.0 mmol/l and diabetes diagnosed by IPH are equally stable states, and we studied the characteristics of the men considered diabetic at baseline who did and did not revert to a nondiabetic status after 30 months of follow-up.

RESEARCH DESIGN AND METHODS

Subjects

The 5,400 Paris policemen studied, aged 44–55 years at baseline, underwent the first annual follow-up examination of the Paris Prospective Study cohort in 1968–1974; these subjects had no cardiovascular disease, were not known to have diabetes, and underwent 2-h 75-g oral glucose tolerance testing. An average of 30 months later, they underwent a second oral glucose tolerance test. The glucose concentrations of these 5,400 men did not differ from the 1,497 men who were present at the baseline examination but did not undergo follow-up examination (data not shown). During the 30 months between the two oral glucose tolerance tests, some men had been diagnosed and treated for diabetes by their own physician. If the men had high fasting glucose concentrations at the baseline examination, they were advised to consult a physician, but no other specific advice was given. In the 1970s, the diagnostic criteria were based on symptoms and fasting glucose concentrations, and the usual cutoff for the diagnosis of diabetes was 7.2 mmol/l (130 mg/dl).

Methods

Glucose and insulin concentrations were determined both at fasting and 2 h postcharge; cholesterol, triglyceride, and nonesterified fatty acid concentrations were

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Abbreviations: FPG, fasting plasma glucose; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; IPH, isolated postchallenge hyperglycemia; WHO, World Health Organization.
A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

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Table 1—*Distribution of the men according to diabetic status at the first and second oral glucose tolerance tests ~30 months later, the Paris Prospective Study*

	Second oral glucose tolerance test				
		Diabetes diagnosed by			
	Nondiabetic	IPH	FPG		
FPG (mmol/l) 2-h glucose (mmol/l)	<7.0 <11.1	<7.0 ≥11.1	≥7.0	Own Physician	Total (*n*)
First oral glucose tolerance test					
Normal/IFG	4,615 (97.3)	8 (0.2)	96 (2.0)	25 (0.5)	4,744
(FPG <7.0 mmol/l; 2-h glucose <7.8 mmol/l)					
IGT					
IGT and non-IFG	247 (94.6)	7 (2.7)	4 (1.5)	3 (1.1)	261
(FPG <6.1 mmol/l; 2-h glucose ≥7.8 and <11.1 mmol/l)					
IGT and IFG	160 (85.1)	1 (0.5)	23 (12.2)	4 (21)	188
(FPG ≥6.1 and <7.0 mmol/l; 2-h glucose ≥7.8 and <11.1 mmol/l)					
Diabetes diagnosed by					
IPH	37 (72.5)	8 (15.7)	4 (7.8)	2 (3.9)	51
(FPG <7.0 mmol/l; 2-h glucose ≥11.1 mmol/l)					
FPG	65 (41.7)	8 (5.1)	65 (41.7)	18 (11.5)	156
≥7.0 mmol/l					
Total (*n*)	5,124	32	192	52	5,400

Data are *n* (%).

determined at fasting. The mean corpuscular volume was used as a marker of excessive alcohol consumption (8). The men were questioned about smoking habits and whether any of their first-degree relatives had diabetes, and BMI and blood pressure were measured.

We have classed the men as follows: *1*) normal 2-h glucose and normal or impaired fasting glucose (normal/IFG): 2-h plasma glucose <7.8 mmol/l and FPG <7.0 mmol/l; *2*) impaired glucose tolerance and normal fasting glucose (IGT and non-IFG): 2-h plasma glucose ≥7.8 and <11.1 mmol/l and FPG <6.1 mmol/l; *3*) impaired glucose tolerance and impaired fasting glucose (IGT and IFG): 2-h plasma glucose ≥7.8 and <11.1 mmol/l and FPG ≥6.1 and <7.0 mmol/l; *4*) diabetes diagnosed by IPH: 2-h plasma glucose ≥11.1 mmol/l and FPG <7.0 mmol/l; *5*) diabetes diagnosed by FPG: FPG ≥7.0 mmol/l.

After the 30 months of follow-up, the men were again classified as nondiabetic or diabetic (diabetes diagnosed by IPH, diabetes diagnosed by FPG, or diabetes diagnosed by their own physician).

Statistical analysis

The characteristics of the men are presented as means (SD) or, for the parameters with a skewed distribution (insulin, triglycerides, nonesterified fatty acids), logarithmic transformations were used and the geometric mean and 95% CI are given. Statistical comparisons were determined by Student's *t* test and χ^2 test. SAS software (Version 8; SAS Institute, Cary, NC) was used for all analyses.

RESULTS

Distribution of subjects on first oral glucose tolerance test

Of the 5,400 men aged 44–55 years at baseline, diabetes was diagnosed in 207 subjects (3.8%): diabetes was diagnosed by FPG in 156 subjects (2.9%) and by IPH in 51 subjects (0.9%) (Table 1). Therefore, diabetes would not be diagnosed in 51 (25%) of these men if only the FPG was measured. In addition, 449 subjects (8.3%) had IGT.

The status of the men 30 months later

An average of 30 months after the first follow-up examination, diabetes was diagnosed in 276 (5.1%) of the men. In 52 (1.0%) of these men, diabetes was diagnosed by a physician; in 192 (3.6%) of the men, diabetes was diagnosed by FPG; and in 32 (0.6%) diabetes was diagnosed by IPH. At baseline, 129 (47%) of these 276 men had been classified as having normal/IFG, 42 (15%) were classified as having IGT, and 105 (38%) were classified as having diabetes.

Among the 52 men in whom diabetes was diagnosed by a physician, 11.5% were diagnosed diabetic by FPG at baseline. In comparison, 3.9% were diagnosed diabetic by IPH at baseline ($P < 0.05$). Both of these incidences were higher than for the other three groups of men studied (Table 1).

Of the 156 men in whom diabetes was diagnosed by FPG at baseline, 65 (42%) were classified as nondiabetic 30 months later. In contrast, of the 51 men in whom diabetes was diagnosed by IPH at baseline, 37 (72%) were classified as nondiabetic 30 months later ($P < 0.0001$).

Characteristics of the men who remained diabetic and the men who reverted to nondiabetic status

In the 51 men in whom diabetes was diagnosed by IPH at baseline (Table 2), only the cholesterol concentration was significantly different between those who remained diabetic and those who reverted to nondiabetic status; the mean concentration was higher in the latter ($P < 0.006$). However, in the men who remained diabetic in comparison with those who reverted, there was a higher prevalence of diabetes in the family ($P < 0.1$), a lower diastolic blood pressure ($P < 0.1$), higher fasting and 2-h glucose concentrations ($P < 0.1$), and a lower mean corpuscular volume ($P < 0.08$).

In contrast, in the 156 men in whom

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Table 2—*Baseline characteristics of men who remained diabetic and men who reverted to nondiabetic status during 30 months of follow-up, according to diagnosis of diabetes by IPH or by FPG at baseline. The Paris Prospective Study*

	Diabetes diagnosed by IPH at baseline			Diabetes diagnosed by FPG at baseline		
	Remained diabetic*	*P*	Reverted to nondiabetic status	Remained diabetic*	*P*	Reverted to nondiabetic status
n	14		37	91		65
Age (years)	49	0.2	48	49	0.1	48
Diabetes in family	14.3%	0.1	2.9%	13.5%	0.4	18.3%
Smokers	71%	0.9	73%	54%	0.6	49%
BMI (kg/m^2)	24.8	0.8	25.1	28.8	0.9	28.9
Systolic blood pressure (mmHg)	157	0.8	159	162	0.5	159
Diastolic blood pressure (mmHg)	80	0.1	86	89	0.6	90
FPG (mmol/l)	6.0	0.1	5.7	8.0	0.002	7.5
2-h glucose (mmol/l)	12.6	0.09	12.0	11.5	0.0001	8.7
Fasting insulin (pmol/l)	69	0.8	65	140	0.4	127
2-h insulin (pmol/l)	380	0.5	439	434	0.4	396
Cholesterol (mmol/l)	4.9	0.006	5.9	5.9	0.6	6.0
Triglycerides (mmol/l)	1.4	0.5	1.2	1.7	0.8	1.8
Nonesterified fatty acids (mmol/l)	141	0.9	142	110	0.2	99
Mean corpuscular volume (≥100 fl)	38%	0.08	67%	38%	0.2	28%

Data are mean or %. *Diagnosed by IPH, diagnosed by FPG, or diagnosed by a physician, see Table 1.

diabetes was diagnosed by FPG at baseline, only the fasting and 2-h plasma glucose concentrations were significantly different. The concentrations were higher in the men who remained diabetic, and these men were, on average, 1 year older ($P < 0.1$). No other factors were close to being significantly different.

CONCLUSIONS — For the men in the Paris Prospective Study in whom diabetes was diagnosed at baseline, 58% diagnosed by FPG were still considered diabetic after 30 months of follow-up, which is significantly higher than the 28% of men in whom diabetes was diagnosed by IPH at baseline. Therefore, as expected, diabetes diagnosed by FPG was more stable. There were significantly more men who had received a diagnosis of diabetes from a physician among those in whom diabetes was initially diagnosed by FPG rather than by IPH (11.5 vs. 3.9%); diagnosis presumably would have been based on at least a second fasting hyperglycemia or following diabetic symptoms. This percentage may be higher because in the men who had high FPG at baseline, diabetes was later diagnosed by their physicians on the basis of a second fasting hyperglycemia.

After the introduction of the new diagnostic criteria, some prospective studies have been published on the progression to diabetes in subjects with IGT or impaired fasting hyperglycemia (9,10).

In addition, two studies (11,12) have looked at reversion to a nondiabetic status for the American Diabetes Association fasting criteria and the 1980 or 1985 WHO criteria (FPG ≥7.8 mmol/l and/or 2-h glucose ≥11.1 mmol/l). The study by Burke et al. (11) comprised a 7- to 8-year follow-up, whereas in the study by de Vegt et al. (12), there was a 2- to 6-week interval between oral glucose tolerance tests. For the fasting criteria (glucose ≥7.0 mmol/l) in these studies, 88 and 74% of the subjects, respectively, remained diabetic, compared with 58% of the men in our study, during a 30-month follow-up. According to the 1985 WHO criteria, Burke et al. and de Vegt et al. found that 84 and 77% of the subjects, respectively, remained diabetic; again, these percentages are much higher than the 43% in the Paris Prospective Study. These figures do not allow us to see the reproducibility of the group with diabetes diagnosed by IPH, but both seem to be much higher than in our study. These differing results are undoubtedly due to the characteristics of the populations studied as well as the different time delays between the two oral glucose tolerance tests in these reports.

We have already shown that, compared with the men in whom diabetes was diagnosed by FPG at baseline, the men in whom diabetes was diagnosed by IPH at baseline had a significantly lower frequency of diabetes in the family as well as significantly lower mean BMI and triglyceride concentrations (13). These are three characteristics that accompany diabetes, lending doubt as to whether diabetes diagnosed by IPH is the same genetic disease as diabetes diagnosed by FPG. Furthermore, the mean corpuscular volume, a marker of alcohol intake, is significantly higher in men with diabetes diagnosed by IPH than in men with diabetes diagnosed by FPG, an indicator of possible behavioral influences on the 2-h hyperglycemia.

In the entire Paris Prospective Study cohort, the frequency of diabetes in the family was 8%, whereas for the men who reverted from diabetes diagnosed by IPH to nondiabetic status, only 3% had a family history of diabetes, which is much lower than the 14% in those who remained diabetic ($P = 0.1$). This would imply that the men with diabetes diagnosed by IPH at baseline, who reverted to a nondiabetic status, had less genetic and more life-style susceptibility than those who remained diabetic. In line with this argument, a high mean corpuscular volume, a marker of high alcohol intake, was much more prevalent in the men who reverted to a nondiabetic status (67 vs. 38%, $P = 0.08$). The mean cholesterol concentration was significantly higher in the 14 men in whom diabetes was initially diagnosed by IPH who remained diabetic compared with the 37 who reverted to

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nondiabetic status. This difference is hard to explain, particularly because only 2 of these 14 men received a diagnosis of diabetes from a physician and could have benefited from dietary advice. Although there was little difference in the characteristics of the reverters and nonreverters in the men in whom diabetes was diagnosed by FPG at baseline, the genetic predisposition to diabetes was relatively high in both groups, with 14 and 18% having a first-degree relative with diabetes. In all cases, those who remained diabetic had higher mean concentrations of both fasting and 2-h glucose concentrations than those who reverted to nondiabetic status.

For the men in the Paris Prospective Study, diabetes diagnosed by one fasting plasma hyperglycemia was more reproducible than diabetes diagnosed by one isolated 2-h hyperglycemia. Other studies are required to verify whether this is specific to our population of men, who were smokers and drinkers: 40% smoked (13) and the average alcohol intake was 49 g of pure alcohol per day (14) (from a study of 446 of these men; this is equivalent to 0.6 l of wine per day).

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