The Natural History of Progression From Normal Glucose Tolerance to Type 2 Diabetes in the Baltimore Longitudinal Study of Aging

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The natural history of progression from normal glucose tolerance (NGT) to impaired fasting glucose (IFG), impaired glucose tolerance (IGT), and type 2 diabetes is not well defined. We studied this progression using biennial oral glucose tolerance tests performed in the Baltimore Longitudinal Study of Aging and survival analysis to assess progression from NGT to abnormal fasting plasma glucose (FPG; ≥6.1 mmol/l), abnormal 2-h plasma glucose (2hPG; ≥7.8 mmol/l), IFG (FPG 6.1–6.9 mmol/l, 2hPG ≤7.8 mmol/l), and IGT (FPG <6.1 mmol/l, 2hPG 7.8–11.0 mmol/l), and from IFG-IGT to diabetes (FPG ≥7.0 mmol/l or 2hPG ≥11.1 mmol/l). At baseline, the 815 subjects had a mean age of 57 years, 35% were women, and 60% had NGT. Of the 488 subjects with NGT, over half were followed for at least 10 years. By 10 years, 14% had progressed to abnormal FPG and 48% to abnormal 2hPG. Of the 267 subjects who progressed to IFG-IGT, 216 had additional follow-up. By 10 years, 8% of these progressed to diabetes by FPG whereas 27% progressed by 2hPG. In subsidiary analyses, we defined "abnormal" FPG as ≥5.55 mmol/l and "diabetic" FPG as ≥6.1 mmol/l, making the baseline prevalence of IFG similar to that of IGT. By these criteria, 43% progressed to abnormal FPG and 43% to abnormal 2hPG by 10 years of follow-up; among subjects developing impaired FPG or 2hPG, 22% progressed to diabetes by FPG whereas 17% progressed by 2hPG at 10 years. Nonetheless, 42% of subjects developing abnormal FPG did not develop abnormal 2hPG, and vice versa. We conclude that, although phenotypic differences in rates of progression are partly a function of diagnostic thresholds, fasting and postchallenge hyperglycemia may represent phenotypes with distinct natural histories in the evolution of type 2 diabetes. *Diabetes* 52: 1475–1484, 2003

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2hPG, 2-h plasma glucose levels; BLSA, Baltimore Longitudinal Study of Aging; FPG, fasting plasma glucose; IFG, impaired fasting glucose; IGT, impaired glucose tolerance; NGT, normal glucose tolerance; OGTT, oral glucose tolerance test; WHO, World Health Organization.

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Type 2 diabetes is occurring in epidemic proportions worldwide (1). This epidemic will translate into excess morbidity and mortality, especially from cardiovascular disease (2). Type 2 diabetes can be prevented or delayed in subjects with impaired glycemia using behavioral modification, metformin, acarbose, or troglitazone (3–6). Understanding the natural history of type 2 diabetes is essential for early detection of prediabetic hyperglycemia and for interrupting the progression from normal to abnormal glucose tolerance.

Impaired fasting glucose (IFG) and impaired glucose tolerance (IGT) represent mildly elevated fasting plasma glucose (FPG) or 2-h plasma glucose (2hPG) levels after an oral glucose tolerance test (OGTT), respectively (7,8). IFG and IGT consistently predict increased risk for diabetes in many populations (9–16). In most studies, IGT is at least as strong a risk factor for diabetes as is IFG (10–13). Further, isolated IGT (that is, IGT with normal FPG levels) is more common than isolated IFG; based on current diagnostic thresholds, 30–60% of subjects with IGT have normal FPG levels (12,17,18). In the U.S., current recommendations for the detection of diabetes rely on measurement of FPG alone (7) and assume that fasting hyperglycemia is an early abnormality in glucose tolerance common to subjects with IFG, those who will develop IGT, and ultimately to all who develop type 2 diabetes. However, few longitudinal data are available to support this assumption. Abandonment of the OGTT may leave undetected a large proportion of subjects at risk for type 2 diabetes, and the World Health Organization (WHO) continues to support use of the OGTT (8).

Current data on the natural history of type 2 diabetes are derived primarily from prospective studies where a baseline OGTT has been followed after 1–11 years by a second OGTT. The data from Pima Indians represent one example where serial OGTTs have been performed; these data demonstrate similar incidence rates of diabetes among equivalent percentiles of the distribution of FPG versus 2hPG (13). Serial FPG levels, measured over about a decade as part of routine care at the Mayo Clinic, were a major predictor of incident diabetes, even within the clearly normal range of <5.5 mmol/l (16). Edelstein and colleagues (14), reporting data from six distinct populations where OGTTs were performed at least twice, found that in all populations, higher levels of FPG and 2hPG predicted progression from IGT to diabetes.

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Current data leave unanswered whether people with initially normal glucose tolerance (NGT) progress directly to diabetes or develop diabetes only after a period of IFG or IGT, or whether people with IFG also eventually develop IGT, or vice versa, before developing diabetes. Although metabolic data suggest there are differences between IFG and IGT in insulin sensitivity, β-cell responsiveness, and hepatic glucose output (19–21), it is unclear whether abnormal FPG or 2hPG represent a phenotypic continuum or distinct phenotypic pathways to diabetes. In this study, we extended prior observations from the Baltimore Longitudinal Study of Aging (BLSA) (14) using serial OGTT data collected from 3 to >10 biennial examinations to determine whether abnormalities in fasting and postchallenge glycemia represent a continuum or distinct pathways in the natural history of type 2 diabetes.

RESEARCH DESIGN AND METHODS

Study subjects. The BLSA is a prospective study of community-dwelling volunteers, largely from the Baltimore, MD, and Washington, DC, areas. The study was begun by the National Institutes of Health in 1958 and has been previously described (22). Participants are primarily Caucasian, middle- and upper-middle-socioeconomic class volunteers ages 21–96 years who return to the Gerontology Research Center in Baltimore approximately every 2 years for examination. The study is an open cohort design, with dropouts replaced to maintain roughly equal numbers of subjects in each 10-year age stratum. A total of about 1,000 subjects were examined at each study cycle. Subjects were included in the current analysis if they had attended at least three examinations and had an OGTT within an 8-year period; subjects were excluded if they had two or fewer OGTTs, or >4 years had elapsed between any two OGTTs. Study subjects provide written informed consent at each examination. The BLSA has continuing approval from the Institutional Review Board of the Johns Hopkins Bayview Medical Center.

Clinical examination. Most (85%) baseline examinations were conducted between 1977 and 1988. Data were collected after an overnight fast; subjects wore a light hospital gown, were not permitted to smoke, and were permitted minimal ad libitum physical activity during the OGTT. Height, weight, and BMI (kg/m^2) were determined. Waist circumference was measured at the minimal abdominal circumference between the lower edge of the ribcage and the iliac crests. Subjects were classified as overweight (or heavier) if their BMI was ≥25 kg/m^2 and with central obesity if their waist circumference was ≥88 cm (women) or ≥102 cm (men) (23). Subjects reporting any first-degree relative with diabetes were classified as having a family history of diabetes. FPG levels were obtained, an OGTT was administered to subjects not known to have diabetes, and 2hPG levels were measured. Subjects were considered to have diabetes if they reported current or past hypoglycemic drug therapy. Subjects who underwent an OGTT before July 1977 received a glucose load of 1.75 g glucose/kg body wt (102 baseline tests and 33 follow-up tests; the average dosage was 143 g). From July 1977 to the end of follow-up for this study, the glucose dosage for the OGTT was 40 g/m^2 body surface area, corresponding to an average dosage of 78 g in men and 68 g in women. Levels of 2hPG from the older 1.75 g/kg test were converted to values that would have been obtained from the newer 40 g/m^2 dosage according to the formula

$$2\text{hPG}_{40\ \text{g/m}^2\ \text{dosage}} = -17.5 + 1.02\ 2\text{hPG}_{1.75\ \text{g/kg dosage}}$$

The conversion formula was obtained by regressing glucose levels (mg/dl) from the 1.75 g/kg test on the levels from the 40 g/m2 test using data from 322 men who received both the 1.75 g/kg and 40 g/m2 body surface area tests.

Glucose tolerance classification. Subjects were classified using baseline OGTT results as having NGT (FPG <6.1 mmol/l and 2hPG ≤7.8 mmol/l), IFG (FPG 6.1–6.9 mmol/l and 2hPG ≤7.8 mmol/l), IGT (FPG <6.1 mmol/l and 2hPG 7.8–11.0 mmol/l), both IFG and IGT (IFG-IGT), or diabetes (FPG ≥7.0 mmol/l or 2hPG ≥11.1 mmol/l). Subjects with diabetes at baseline were removed from further consideration in this analysis. The remainder were followed with serial OGTTs over subsequent biennial examinations. Subjects with baseline NGT were followed for the development of abnormal FPG (≥6.1 mmol/l) and/or abnormal 2hPG (≥7.8 mmol/l), as well as for IFG-IGT and/or diabetes. Subjects with IFG-IGT at baseline, or with IFG-IGT at follow-up after NGT at baseline, were followed for subsequent development of diabetes, as defined by OGTT results. Although we did not count medication-treated diabetes as an outcome, of the 12 subjects (5 with NGT and 7 with IFG-IGT at baseline) who developed medication-treated diabetes, 10 had diabetes by OGTT before treatment and consequently were accurately counted as incidence cases of diabetes. In subsidiary analyses, we also assessed progression to a lower "abnormal" FPG level of ≥5.55 mmol/l (≥100 mg/dl) and a lower "diabetic" FPG level of ≥6.1 (≥110 mg/dl), with "normal" FPG set at <5.55 mmol/l. These thresholds were selected to provide similar baseline prevalences of "impaired FPG" (FPG 5.55–6.09 mmol/l and 2hPG ≤ 7.8 mmol/l; 15.5%), "impaired 2hPG" (FPG <5.55 mmol/l and 2hPG 7.8–11.0 mmol/l; 14.1%), "diabetic FPG" (8.8%), and "diabetic 2hPG" (≥11.0 mmol/l; 7.4%). Subsidiary analyses examined whether the rates of progression to abnormal FPG compared with abnormal 2hPG were a function of the relative stringency of FPG criteria versus 2hPG criteria.

Analytical methods. We used Kaplan-Meier product limit estimates, which account for the variable lengths of follow-up, to assess the cumulative incidence of abnormal FPG and 2hPG. Subjects were classified with abnormal FPG and/or 2hPG at the first exam where the level became abnormal, and in our primary analyses remained so categorized even if they had a normal FPG or 2hPG level at a later exam. In subsidiary analyses, we enumerated the number of subjects who reverted to NGT after developing IFG-IGT. In addition, subjects with NGT at baseline who first developed an impaired FPG or 2hPG also were followed subsequently for development of diabetic FPG or 2hPG. We further stratified Kaplan-Meier analyses of progression from normal to abnormal glucose levels by diabetes risk factor categories and used the log rank test to compare differences in Kaplan-Meier estimates between strata (24). Annualized glucose tolerance progression rates were estimated by dividing the number of outcomes by the person-years of follow-up in each category; 95% CIs were estimated using a Poisson error distribution (25). Contrasts between annualized progression rates in risk factor strata were tested using type III likelihood ratio statistics. We conducted analyses using SAS software, and defined statistical significance as $P < 0.05$ (26).

TABLE 1
Baseline characteristics of nondiabetic study subjects

	NGT	IFG-IGT
n	488	265
Mean age (years)	52.9 ± 16.6	61.8 ± 14.0
Women	192 (39.3)	74 (27.9)
Caucasian	468 (95.9)	252 (95.1)
Age 65 years or older	128 (26.2)	129 (48.7)
1st degree relative with diabetes	122 (25.0)	76 (28.7)
BMI ≥25 kg/m^2	173 (35.5)	158 (59.6)
Waist circumference ≥88 cm (women) or ≥102 cm (men)	29 (6.0)	46 (17.2)
Follow-up		
Mean duration (years)	11.4 ± 5.3	10.2 ± 5.0
At least 6 years	404 (82.7)	203 (76.6)
At least 10 years	268 (54.9)	117 (44.2)
At least 16 years	122 (25.0)	41 (15.5)
At least 20 years	32 (6.6)	12 (4.5)

*Data are *n* (%) or means ± SD.

RESULTS

Of 815 subjects ages 20–89 years at baseline, 488 (60.0%) had NGT and 265 (32.5%) had IFG-IGT; 62 (7.6%) had diabetes and were not considered further (Table 1). Of the 488 subjects with NGT at baseline, 209 (42.8%) remained with NGT and 279 progressed to abnormal glucose tolerance after an average of 11 years of observation (Fig. 1*A*). We found that 10 times as many NGT subjects progressed to abnormal 2hPG alone (191; 39.1%) compared with progression to abnormal FPG alone (19; 3.9%). Of the 30 subjects who initially developed abnormal FPG, 11 (37%) subsequently developed abnormal 2hPG, whereas of the 225 initially developing abnormal 2hPG, only 34 (15%) subsequently developed abnormal FPG. Of the 69 subjects who developed both abnormal FPG and abnormal 2hPG,

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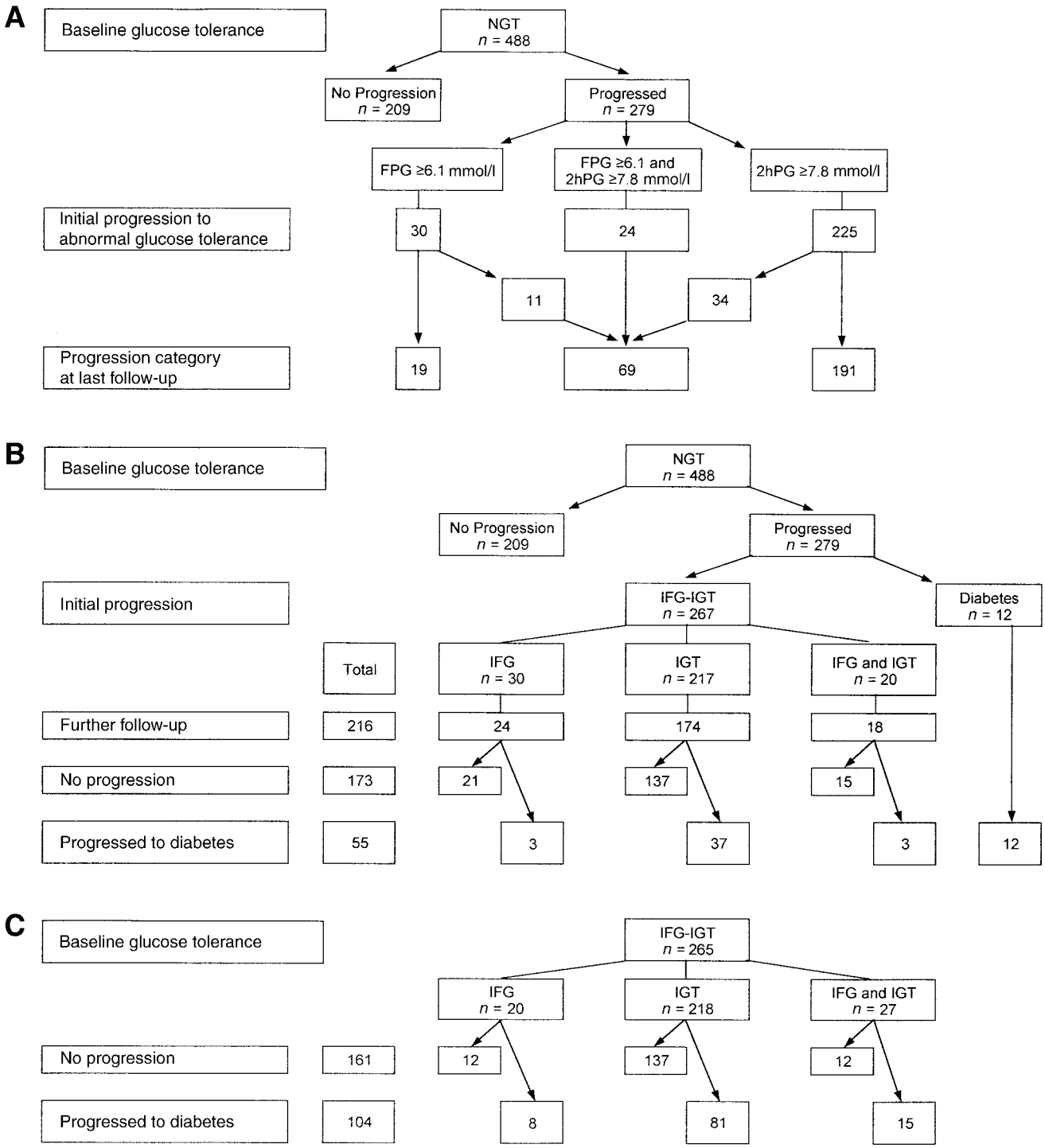

FIG. 1. Distribution of glucose tolerance categories at baseline and follow-up using standard diagnostic categories. *A*: Overall numbers of subjects progressing to abnormal FPG (≥ 6.1 mmol/l) and/or abnormal 2hPG (≥7.8 mmol/l) from NGT at baseline. *B*: Overall numbers of subjects progressing to diabetes by FPG (≥7.0 mmol/l) and/or 2hPG (≥11.1 mmol/l) from IFG and/or IGT after NGT at baseline. *C*: Overall numbers of subjects progressing to diabetes by FPG (≥7.0 mmol/l) and/or 2hPG (≥11.1 mmol/l) from IFG and/or IGT at baseline.

24 (35%) first demonstrated both these abnormalities at the same exam.

Longitudinal progression from NGT to abnormal FPG and 2hPG is displayed in Fig. 2*A*. By 5 years of follow-up, 31.1% had progressed to abnormal 2hPG, whereas only 7.4% had progressed to abnormal FPG (Table 2); by 20 years of follow-up, the proportions were 71.1 and 38.7%, respectively. The annualized progression rate from NGT to abnormal 2hPG was about four times the rate of progression from NGT to abnormal FPG (Table 2). Annualized progression rates stratified by age, sex, obesity, and family history of diabetes are also shown in Table 2. Subjects older than age 65 years had substantially accelerated rates of progression to abnormal 2hPG compared with younger

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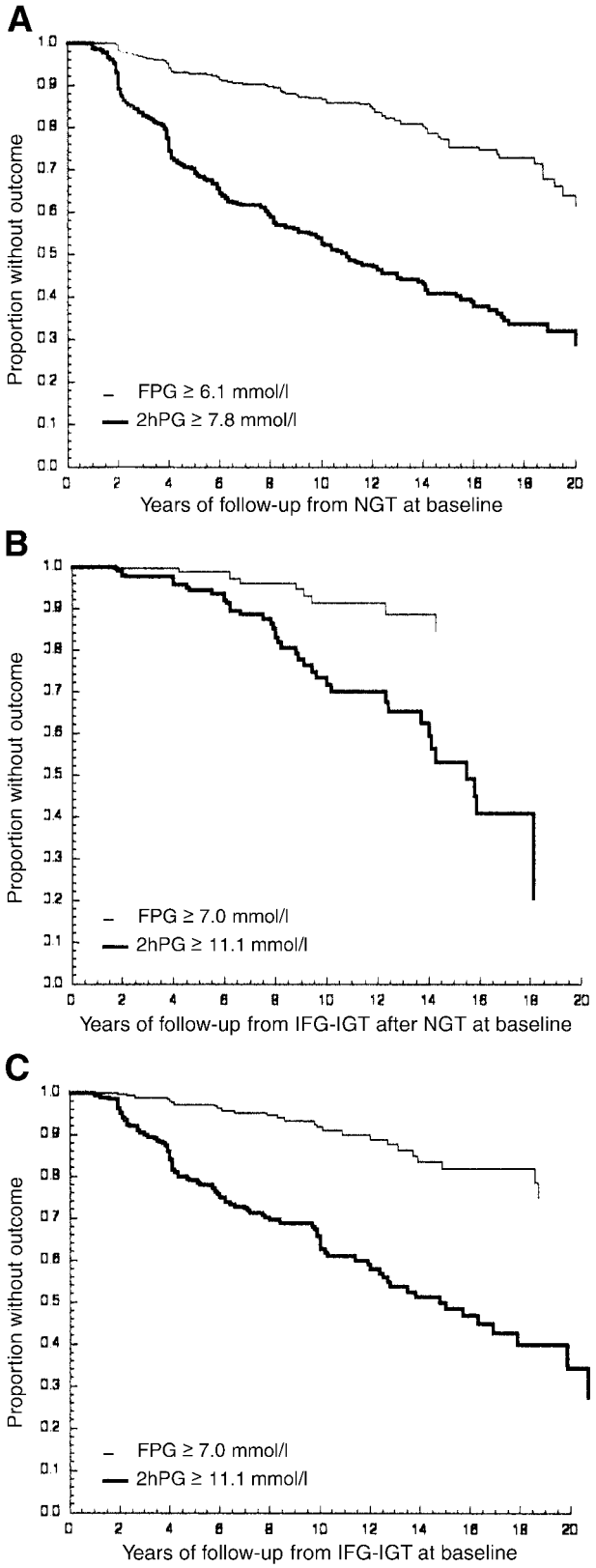

FIG. 2. Kaplan-Meier curves showing the cumulative proportion of subjects progressing from normal to abnormal glucose tolerance using standard diagnostic criteria. *A*: Progression from NGT to abnormal FPG (≥6.1 mmol/l) and abnormal 2hPG (≥7.8 mmol/l) among 488 subjects. *B*: Progression from IFG-IGT after NGT baseline to diabetic FPG (≥7.0 mmol/l) and diabetic 2hPG (≥11.1 mmol/l) among 216 subjects. *C*: Progression from IFG-IGT at baseline to diabetic FPG (≥7.0 mmol/l) and diabetic 2hPG (≥11.1 mmol/l) among 265 subjects.

subjects, but older and younger subjects had similar rates of progression to abnormal FPG. Men progressed to abnormal FPG or 2hPG more rapidly than women, as did subjects with overall or central obesity compared with lean subjects. A family history of diabetes did not modify rates of progression to abnormal glucose tolerance.

The number of subjects progressing from NGT to IFG-IGT to diabetes is displayed in Fig. 1*B*. Of these NGT subjects, 12 (2.5%) developed diabetes as the initial OGTT abnormality (none by FPG alone) and another 267 progressed to IFG-IGT. Of these, 216 had additional subsequent follow-up (6 ± 5 years [mean ± SD]; 46.4% had at least 6, 19.9% had at least 10, and 9.4% had at least 14 additional years). Of these 216, 43 subjects (8.8% of 488 and 16.1% of 267) progressed to diabetes. Among 265 subjects with IFG-IGT at baseline (Fig. 1*C*), 104 (39.3%) progressed to diabetes. Substantially more subjects with IFG-IGT (either at baseline or after NGT at baseline) progressed to diabetes by 2hPG compared with progression by FPG. Progression to diabetes by FPG was a rare event that typically occurred in combination with progression by 2hPG.

Longitudinal progression from IFG-IGT to OGTT-defined diabetes is displayed in Fig. 2 and annualized progression and cumulative incidence rates are shown in Table 2. As in the case of progression from normal to abnormal glucose tolerance, rates of progression from IFG-IGT to diabetes (Fig. 2*B* and *C*) were substantially more rapid for 2hPG compared with FPG. In addition, subjects with IFG-IGT at baseline progressed to diabetes somewhat more rapidly than subjects developing IFG-IGT from NGT. Overall, the 5-year cumulative incidence of diabetic FPG after NGT at baseline was 0.22% and the 10-year cumulative incidence was 1.48%. The 5-year cumulative incidence of diabetic 2hPG after NGT at baseline was 2.11% and the 10-year cumulative incidence was 7.01%.

Results of subsidiary analyses using lower FPG thresholds for abnormal FPG and diabetic FPG are shown in Figs. 3 and 4 and Table 3. When thresholds for abnormal or diabetic FPG were set to approximate the baseline prevalence of abnormal or diabetic 2hPG, the longitudinal probability of developing FPG versus 2hPG outcomes became virtually identical. Only among older subjects was the development of abnormal 2hPG substantially more rapid (11.1 events per 100 person-years) than the development of abnormal FPG (6.7 events per 100 person-years) (Table 3). Rates of progression to the subsidiary "abnormal" states were accelerated by male sex and obesity, with similar effects as in the primary analysis (not shown).

Although in the primary analysis subjects were considered to have had progression of glucose tolerance at the first follow-up OGTT that exceeded specified thresholds, we also examined reversion to NGT among subjects initially progressing to IFG or IGT. Of 72 initially NGT subjects who developed IFG on at least one follow-up OGTT, IFG was detected at the last OGTT in only 12 subjects. For the remaining 60 subjects with follow-up after developing IFG, 42 (70% of 60) had a normal FPG on the next OGTT. Of the 248 subjects developing IGT on at least one follow-up OGTT, IGT was detected at the last OGTT in 49 subjects. For the remaining 199 subjects with

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TABLE 2
Annualized rates of progression to abnormal glucose tolerance

NGT	Progression to FPG ≥6.1 mmol/l				Progression to 2hPG ≥7.8 mmol/l			
	Outcomes (n)	Person-years	Rate/100	95% CI	Outcomes (n)	Person-years	Rate/100	95% CI
Overall	88	5,151	1.71	1.38–2.09	260	4,039	6.44	5.69–7.25
5-year cumulative incidence		7.4				31.1		
10-year cumulative incidence		13.5				47.5		
Age								
≥65 years	20	1,001	2.00	1.25–3.01	84	696	12.1	9.67–14.83
<65 years	68	4,151	1.64	1.28–2.06	176	3,343	5.27	4.53–6.08
P			0.4				<0.0001	
1st degree relative with diabetes								
Yes	28	1,378	2.03	1.37–2.88	73	1,049	6.96	5.48–8.68
No	60	3,773	1.59	1.22–2.03	187	2,990	6.25	5.40–7.19
P			0.3				0.4	
Sex								
Female	20	2,085	0.96	0.60–1.44	82	1,705	4.81	3.84–5.93
Male	68	3,066	2.22	1.73–2.79	178	2,334	7.63	6.56–8.80
P			0.0004				0.0004	
Overall obesity								
BMI ≥25 kg/m^2	47	1,774	2.65	1.96–3.48	118	1,249	9.45	7.85–11.26
BMI <25 kg/m^2	41	3,377	1.21	0.88–1.62	142	2,790	5.09	4.30–5.97
P			0.0003				<0.0001	
Central obesity								
Waist ≥88 (women) or 102 cm (men)	8	240	3.34	1.53–6.21	21	168	12.5	7.88–18.61
Waist <88 (women) or 102 cm (men)	78	4,864	1.60	1.27–1.99	235	3,829	6.14	5.39–6.96
P			0.07				0.01	
IFG-IGT	**Progression to FPG ≥7.0 mmol/l**				**Progression to 2hPG ≥11.1 mmol/l**			
IFG-IGT after NGT at baseline	10	1,552	0.64	0.32–1.13	41	1,480	2.77	2.01–3.71
5-year cumulative incidence		1.2				5.7		
10-year cumulative incidence		8.8				28.4		
IFG-IGT at baseline	26	2,647	0.98	0.65–1.41	101	2,192	4.61	3.77–5.56
5-year cumulative incidence		2.8				21.0		
10-year cumulative incidence		8.3				37.4		

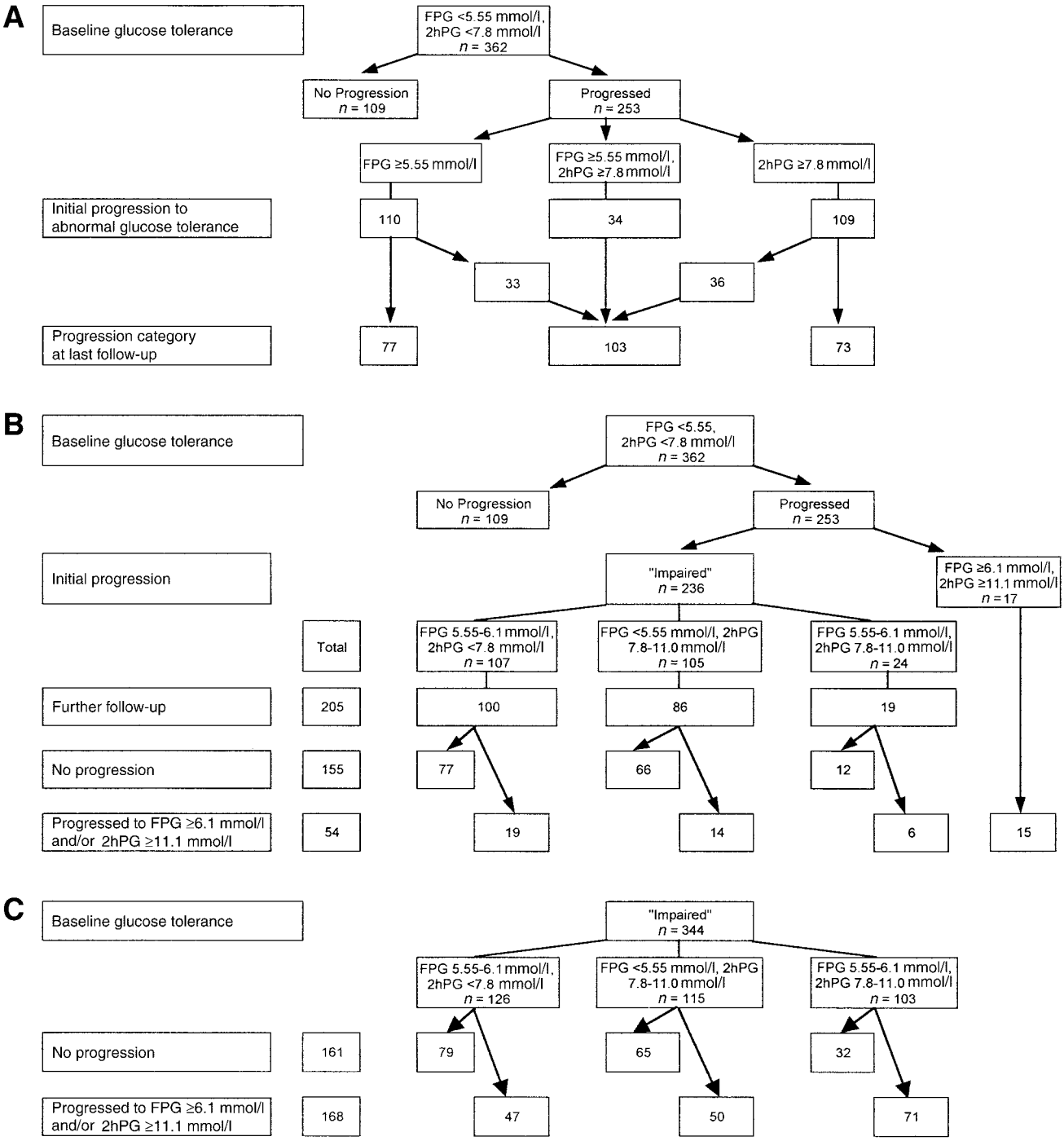

FIG. 3. Distribution of glucose tolerance categories at baseline and follow-up using a lower diagnostic threshold for FPG. *A*: Overall numbers of subjects progressing to abnormal FPG (≥5.55 mmol/l) and/or abnormal 2hPG (≥7.8 mmol/l) from normal glucose tolerance at baseline. *B*: Overall numbers of subjects progressing to diabetes by FPG (≥6.1 mmol/l) and/or 2hPG (≥11.1 mmol/l) from IFG (FPG 5.55–6.09 mmol/l) and/or IGT after NGT at baseline. *C*: Overall numbers of subjects progressing to diabetes by FPG (≥6.1 mmol/l) and/or 2hPG (≥11.1 mmol/l) from IFG and/or IGT at baseline.

follow-up after developing IGT, 103 (52% of 199) had a normal 2hPG on the next OGTT. Using the lower FPG cut-points of ≥5.55 mmol/l defining "impaired" and ≥6.1 mmol/l defining "diabetic," of 154 initially "NGT" subjects developing FPG ≥5.55 mmol/l on at least one follow-up OGTT, FPG ≥5.55 mmol/l was detected at the last OGTT in 19 subjects. For the remaining 135 subjects with follow-up after developing FPG ≥5.55 mmol/l, 83 (62% of 135) had a "normal" FPG on the next OGTT. Of the 153 subjects developing FPG ≥6.1 mmol/l on at least one follow-up OGTT, FPG ≥6.1 mmol/l was detected at the last OGTT in 31 subjects. For the remaining 122 subjects with follow-up after developing FPG ≥6.1 mmol/l, 67 (55% of 122) had a "normal" 2hPG on the next OGTT. Thus, although reversion to NGT seemed to be a little more common from IFG than from IGT, the difference between reversion rates was a function of the stringency of thresholds defining abnormal glycemia.

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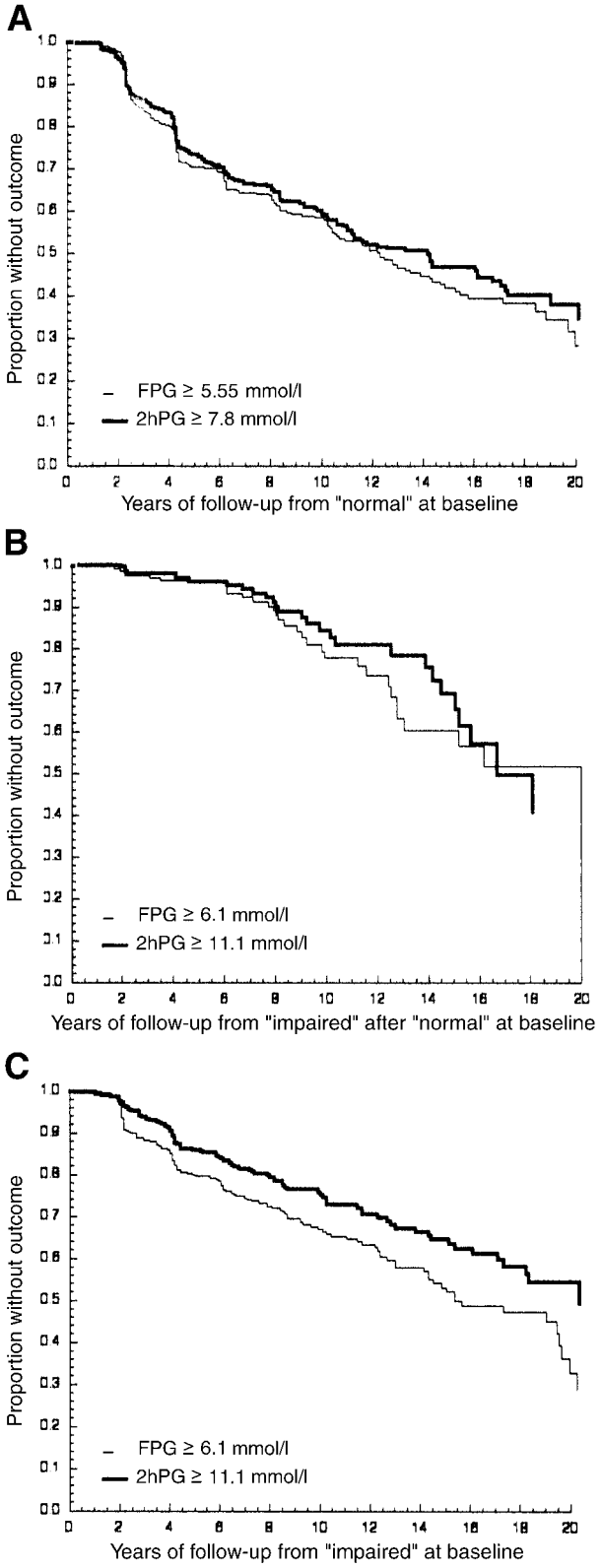

FIG. 4. Kaplan-Meier curves showing the cumulative proportion of subjects progressing from "normal" to "abnormal" glucose tolerance using a lower diagnostic threshold for FPG. *A*: Progression from "normal" glucose tolerance to "abnormal" FPG (≥5.55 mmol/l) and abnormal 2hPG (≥7.8 mmol/l) among 362 subjects. *B*: Progression from "impaired" fasting or 2-h glucose levels after "normal" glucose tolerance at baseline to "diabetic" FPG (≥6.1 mmol/l) and diabetic 2hPG (≥11.1 mmol/l) among 236 subjects. *C*: Progression from "impaired" fasting or 2-h glucose levels at baseline to "diabetic" FPG ≥6.1 mmol/l) and diabetic 2hPG (≥11.1 mmol/l) among 344 subjects.

DISCUSSION

This analysis of more than 20 years of biennial OGTT data from the BLSA suggests that differences in the natural history of impairment of fasting versus postchallenge glycemia are in part a function of diagnostic thresholds defining abnormal, but also suggests at least two distinct phenotypic pathways in the evolution of type 2 diabetes. Based on current American Diabetes Association or WHO criteria for impaired and diabetic glucose tolerance, the more common pathway appeared to be the development of abnormal 2hPG levels with normal FPG levels. This pathway typically featured a prolonged decay in glucose tolerance, with slow progression from NGT to IGT to diabetic 2hPG. In only a few cases did subjects on this pathway manifest IFG or diabetic FPG. The less common, and even slower, pathway included development of IFG and, even more rarely, development of diabetic FPG levels. However, virtually all of these subjects also developed IGT or diabetic 2hPG, and often an elevated 2hPG was the only abnormality diagnostic of type 2 diabetes. These two phenotypes, abnormal 2hPG alone or abnormal FPG in combination with 2hPG, were apparent in the progression from both NGT to impaired FPG and 2hPG and impaired to diabetic glucose tolerance. However, when the threshold for abnormal FPG was defined so that its prevalence approximated the prevalence of abnormal 2hPG, these differences in frequency and rate of progression of the two phenotypes virtually disappeared. Rates of progression to impaired or diabetic FPG were indistinguishable from rates of progression to IGT or postchallenge diabetes. However, in many cases the two pathways remained exclusive; about 42% of subjects developing abnormal FPG did not also develop abnormal 2hPG, and vice versa. In addition, regardless of the threshold defining abnormal, serial OGTT data revealed that at the population level, progression to type 2 diabetes unfolded over the course of decades, often involving a lengthy state of impaired glucose homeostasis before development of diabetes. Development of diabetes within 2 years of NGT was a relatively unusual event. Still, even after prolonged follow-up, many subjects with IFG or IGT had not developed diabetes, and many had reverted to NGT. Standard risk factors for type 2 diabetes, including older age, male sex, and obesity, all accelerated rates of progression from normal to abnormal glucose tolerance. Thus, although current standard diagnostic criteria generate fasting and postchallenge glycemic phenotypes that progress from normal to abnormal at distinctly different rates, alternative criteria produce phenotypes with indistinguishable rates of progression to abnormal. However, our finding that substantial numbers of subjects developed a fasting abnormality but not a postchallenge abnormality (regardless of diagnostic thresholds), and vice versa, supports the hypothesis that progression in these measures toward diabetic thresholds may represent distinct phenotypes in the pathogenesis of type 2 diabetes.

Maintenance of normoglycemia results from a balance between glucose production and disposal mediated by skeletal muscle, pancreatic β-cells, and the liver (27). Disordered physiology in diverse tissue compartments suggests that there should be distinct phenotypes predisposing to type 2 diabetes. Several studies using standard

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TABLE 3
Annualized rates of progression to abnormal glucose tolerance defined by lower FPG thresholds

FPG <5.55 mmol/l, 2hPG <7.8 mmol/l at baseline	Progression to FPG ≥5.55 mmol/l				Progression to 2hPG ≥7.8 mmol/l			
	Outcomes (*n*)	Person-years	Rate/100	95% CI	Outcomes (*n*)	Person-years	Rate/100	95% CI
Overall	180	2,838	6.12	5.27–7.07	176	3,179	5.53	4.76–6.40
5-year cumulative incidence			29.9				27.9	
10-year cumulative incidence			43.3				42.5	
Age								
≥65 years	37	549	6.74	4.80–9.16	56	507	11.1	8.40–14.20
<65 years	143	2,390	5.98	5.06–7.02	120	2,672	4.49	3.73–5.34
P			0.5				<0.0001	
FPG 5.55–6.09 mmol/l, 2hPG 7.8–11.0 mmol/l at baseline	Progression to FPG ≥6.1 mmol/l				Progression to 2hPG ≥11.1 mmol/l			
"Impaired" after "normal" at baseline	33	1,484	2.22	1.55–3.07	28	1,539	1.82	1.23–2.58
5-year cumulative incidence			4.4				4.0	
10-year cumulative incidence			21.8				17.0	
"Impaired" at baseline	126	3,006	4.19	3.50–4.97	96	3,162	3.03	2.47–3.68
5-year cumulative incidence			19.9				13.7	
10-year cumulative incidence			33.4				26.6	

diagnostic criteria have shown that both insulin resistance and impaired first-phase insulin secretion are independent determinants of progression from NGT to IGT and from IGT to diabetes (28–31). Analyses comparing isolated IFG with isolated IGT suggest that variations in insulin resistance or insulin secretion may produce clinically distinct prediabetic phenotypes. Weyer and colleagues (32) found that Pima Indians with IFG or IGT were equally insulin resistant, but those with isolated IFG had a greater impairment in first-phase insulin secretion and higher basal hepatic endogenous glucose output compared with subjects with isolated IGT. Furthermore, among Pimas with IGT, only those with a relatively greater defect in first-phase insulin secretion subsequently developed type 2 diabetes (33). Hepatic endogenous glucose output is a major determinant of FPG levels and in Pimas did not predict diabetes independent of insulin secretion and insulin resistance (28). Davies et al. (21) reported similar observations in nondiabetic Caucasian subjects, where those with IFG and IGT had equivalent insulin resistance, but those with IFG had depressed β-cell function, as assessed using homeostasis model assessment. In a study of nondiabetic relatives of type 2 diabetic patients in Finland, Tripathy and colleagues (20) concluded that IFG and IGT represent distinct stages in the evolution of abnormal glucose tolerance, but in contrast to the Weyer et al. (32) and Davies et al. (21) reports, the Finnish subjects with IGT had relatively impaired β-cell function compared with subjects with IFG. These analyses contrasting IFG with IGT were cross-sectional and used standard thresholds for impaired FPG and 2hPG. It remains to be demonstrated that these apparent phenotypic differences persist even when diagnostic thresholds are adjusted to a similar degree of stringency. The longitudinal data from the BLSA suggest that the prevalence of these phenotypes and their rates of progression to hyperglycemia are dependent on the stringency of diagnostic thresholds; the degree of physiological differences among phenotypes may also be a function of diagnostic stringency. The BLSA data also suggest that impaired FPG and 2hPG levels are not necessarily discrete stages along a continuum in the evolution of hyperglycemia, but may represent distinct underlying physiological phenotypes that evolve to diabetes with distinct natural histories.

Longitudinal serial glucose tolerance testing also provides detailed data on rates of progression from NGT to IFG, IGT, and diabetes in a population at low risk for diabetes. Among BLSA subjects with NGT at baseline, the 5 year cumulative incidence rates of diabetic FPG (0.22%) or diabetic 2hPG (2.1%) were an order of magnitude lower than 5-year rates of progression among subjects with IFG-IGT at baseline (diabetic FPG, 2.8%; diabetic 2hPG, 21%). The 5-year rates of progression to diabetes after development of IFG-IGT from NGT were also lower (diabetic FPG, 1.2%; diabetic 2hPG, 5.7%) than from IFG-IGT at baseline. These data suggest that groups with IFG-IGT on first examination contain subjects already close to transitioning to diabetes, and imply that at the population level, diabetes develops slowly over many years, transitioning through a prolonged state of impaired glycemia. Mayo Clinic data (16) of serial, apparently fasting levels of plasma glucose have shown that diabetes develops from

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impaired glycemia at a fairly constant rate over many years. The Mayo data also showed that the rate of developing of diabetes was a function of diagnostic thresholds defining baseline abnormal; 5-year cumulative incidence rates of developing FPG ≥7.0 mmol/l were 7, 19, and 39% for subjects with initial FPG levels in the ranges of <5.6, 5.6–6.0, and 6.1–6.9 mmol/l, respectively. In the prior analysis by Edelstein and colleagues of BLSA data (14), the diabetes incidence rate from IFG and IGT was 6.1 per 100 person-years. Our current findings suggest that progression from IGT contributes more to diabetes incidence than does progression from IFG, but that this relative difference was largely a function of the threshold defining IFG. In the Hoorn Study of two OGTTs measured an average of 6.4 years apart, the cumulative incidence of diabetes was similar comparing isolated IFG with isolated IGT (33 vs. 34%, respectively) (11). However, in Pima Indians, the 5-year cumulative incidence of diabetes was lower from isolated IFG than from isolated IGT (20 vs. 31%, respectively) (13). These studies and our present analysis raise the question of what is the "right" threshold for defining IFG as a risk factor for type 2 diabetes. In the Pima data, a FPG threshold of 5.7 mmol/l produced a similar predictive power for diabetes, as did a 2hPG threshold of 7.8 mmol/l (13). This threshold is similar to our alternative threshold of 5.55 mmol/l and suggests that perhaps the "right" threshold defining IFG might be closer to 5.5–5.7 mmol/l (100–103 mg/dl) than 6.1 mmol/l. It should be noted that, overall, diabetes incidence rates in the BLSA were substantially lower than those reported in these other prospective studies of type 2 diabetes. This was likely a function of the primarily Caucasian, middle-class source population, a "survivor effect" magnified by the open cohort study design, and the variable glucose dosage (graded by body weight or surface area) and the carefully controlled conditions under which the OGTTs were performed. Despite these methodological differences, our analysis supports the idea that type 2 diabetes usually develops at a relatively constant rate over many years from normal through impaired glycemia, and that the rate of this progression is a function of thresholds used to define abnormal glycemia.

Age, family history of diabetes, and both overall and central obesity have been previously defined as risk factors for progression from IFG-IGT to diabetes in this and other studies (14). In the present analysis, we found that male sex and obesity accelerated progression from NGT to abnormal FPG and abnormal 2hPG, but that family history did not modify progression from normal to abnormal glycemia. Interestingly, we found that older age did not modify the rate of progression from NGT to abnormal FPG, but did have a substantial effect on rates of progression to abnormal 2hPG, regardless of the stringency of the threshold used to define abnormal FPG. If an elevated 2hPG level reflects insulin resistance with relatively preserved β-cell function (32), our finding is consistent with the observation that aging is associated with a greater degree of progressive insulin resistance than with progressive impairment of insulin secretion (34).

In conclusion, data from more than two decades of serial glucose tolerance testing in Caucasian subjects of the BLSA suggest that fasting and postchallenge hyperglycemia may represent distinct phenotypic pathways to the development of type 2 diabetes. Apparent differences in the prevalence and natural history of IFG and IGT are partly a function of different diagnostic thresholds. Nonetheless, many subjects progressing from NGT to IGT and diabetic 2hPG do not develop abnormal FPG levels and, likewise, subjects progressing to diabetes by FPG may not always develop abnormal 2hPG levels. These data suggest that abnormal FPG and 2hPG levels are not necessarily part of a continuum in the evolution of hyperglycemia. The data also show that the evolution of these phenotypes from normal to diabetes occurs, in most cases, at a fairly constant rate over many years. These findings may have prevention implications. We now know that type 2 diabetes is preventable when subjects with impaired glycemia are detected and treated (3–6). Detection programs relying solely on elevated FPG levels using current diagnostic thresholds may only detect the more uncommon IFG phenotype, and miss a substantial number of subjects at risk for diabetes on the basis of abnormal 2hPG levels. Specifying a lower "abnormal" FPG level (in the 5.55–5.7 mmol/l range), using the OGTT, or identifying clusters of insulin resistance−related traits (35) may be required to maximize identification of subjects at risk for developing type 2 diabetes. Persistence of impaired glycemia over many years suggests that identifying these subjects for intervention should be relatively straightforward to implement on a clinical or population basis.

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