Analysis of Metabolic Progression to Type I Diabetes in ICA$^+$ Relatives of Patients With Type I Diabetes

David Bleich, MD
Richard A. Jackson, MD
J. Stuart Soeldner, MD
George S. Eisenbarth, MD, PhD

We intensively studied 5 islet cell–antibody–positive (ICA$^+$) first-degree relatives of type I (insulin-dependent) diabetic patients before overt diabetes. In total, 55 intravenous glucose tolerance tests (IVGTTs) and 83 fasting plasma glucose determinations were made over a maximum 4-yr period before diabetes. The 5 prediabetic relatives (not diabetic when initially studied but subsequently progressed to overt diabetes) as a group showed a progressive rise in fasting glucose ($r = 0.58$, $P < 0.001$, slope = 23.1 mg · dl^{-1} · yr^{-1}) and glucose at 60 min in IVGTT ($r = 0.46$, $P = 0.01$, slope = 47.5 mg · dl^{-1} · yr^{-1}) beginning 1.5 yr before diabetes. During the 4.0- to 1.5-yr period before overt diabetes, no change was observed in fasting glucose or glucose at 60 min on IVGTT (fasting glucose: $r = 0.21$, $P = 0.18$, slope = 2.1 mg · dl^{-1} · yr^{-1}; 60-min glucose: $r = 0.08$, $P = 0.72$, slope = 2.9 mg · dl^{-1} · yr^{-1}). The positive predictive value for a fasting glucose >108 mg/dl to be within 1.5 yr of diabetes was 100% (11 of 11 values). The negative predictive value of a stimulated insulin (1-min + 3-min insulin − 2 × basal insulin) level >24 μU/ml to be >1.5 yr from diabetes was 90% (9 of 10 values) and 100% (10 of 10 values) at >1 yr from overt diabetes. We tested these predictive values by applying fasting glucose >108 mg/dl and stimulated insulin >24 μU/ml to another prediabetic group ($n = 14$) not included in the original analysis because each individual had fewer measurements. Once again, the positive predictive value that diabetes would develop within 1.5 yr from the time of fasting glucose >108 mg/dl was 100% (5 of 5 values), and the negative predictive value of stimulated insulin >24 μU/ml was 63% (5 of 8 values) for 1.5 yr and 89% (6 of 7 values) for 1 yr. Finally, 16 ICA$^+$ relatives who had not yet become diabetic lacked raised fasting glucose levels (14 of 16 patients) and had stimulated insulin levels >24 μU/ml. *Diabetes Care* 13:111–18, 1990

As recently reviewed, the hypothesis that type I (insulin-dependent) diabetes is an autoimmune disease appears to be widely accepted (1). There is controversy, however, concerning the process leading to hyperglycemia. The notion that diabetes is an acute event has come under scrutiny because studies of an immunologic prodromal phase and loss of first-phase insulin secretion point to a chronic progressive process that comes before overt disease (2–7). In this study, we describe a progressive loss of glucose homeostasis in most patients before overt type I diabetes. In addition, we found 2 of 19 patients who did not have loss of stimulated insulin secretion on intravenous glucose tolerance test (IVGTT) before overt hyperglycemia. Results presented herein are part of an ongoing study of first-degree relatives of type I diabetic patients and monozygotic sets of twins (1 with type I diabetes) who were selected by screening for cytoplasmic islet cell antibodies. We initially analyzed the prediabetic period in 5 patients (aged 8–66 yr) chosen from a group of 19 prediabetic patients because they had numerous fasting glucose and IVGTT measurements. We developed predictive parameters and then tested these parameters with data from the remaining prediabetic patients in our study population. We emphasize that all conclusions in this study are preliminary due to the few highly selected patients and may apply only to patients with islet cell antibodies (ICAs) or to first-degree relatives.

From the Joslin Diabetes Center, Brigham and Women's Hospital, New England Deaconess Hospital, and Harvard Medical School, Boston, Massachusetts; and the University of California, Davis, Sacramento, California.

Address correspondence and reprint requests to George S. Eisenbarth, MD, PhD, Joslin Diabetes Center, One Joslin Place, Boston, MA 02215.

Received for publication 5 December 1988 and accepted in revised form 6 April 1989.

RESEARCH DESIGN AND METHODS

High-risk relatives were identified by means of an ICA screening program at the Joslin Diabetes Center, Boston, MA. Each relative identified as positive had a cytoplasmic ICA concentration >40 Juvenile Diabetes Foundation U. Glucose determinations were made with a Beckman Glucose Analyzer and are given for plasma glucose in milligrams per deciliter. Insulin was measured by a double-antibody radioimmunoassay. IVGTTs were performed by infusing 0.5 g/kg glucose over a 2- to 3-min period (8). We measured basal, 1-, and 3-min insulin levels to calculate stimulated insulin secretion. This was conducted by taking the 1-min + 3-min insulin concentration and subtracting two times the basal insulin level. With this calculation, the 1st percentile of stimulated insulin secretion in a nondiabetic population of 225 subjects was 24 μU/ml.

A patient was considered to have overt diabetes when fasting plasma glucose was >140 mg/dl or random glucose was >200 mg/dl. All overt diabetic patients in this study developed random hyperglycemia, elevated HbA_{1c}, and were receiving insulin treatment. Five patients residing in Massachusetts (intensively studied group) had frequent fasting glucose determinations and IVGTTs until they developed overt hyperglycemia. In total, 83 fasting glucose measurements and 55 IVGTTs were performed before diabetes on the five patients. Table 1 describes the five intensively studied patients at the time of initial study.

A second set of prediabetic patients (having fewer tests per individual) was used to test the positive and negative predictive values derived from the data analysis on the original 5 patients. This second group consisted of 14 ICA^+ patients ranging in age from 2.5 to 58 yr. Table 2 shows the details of these patients at time of registry into our prediabetes study. Finally, 16 ICA^+ relatives identified in an identical manner who have not yet progressed to diabetes were analyzed.

Linear regression analysis was performed on the data for the following variables: fasting glucose versus years to overt type I diabetes mellitus, glucose at 60 min on IVGTT versus years to type I diabetes, and stimulated insulin secretion versus years to type I diabetes. All graphing and analysis was conducted on the Clinfo computer system. The plots of fasting glucose and glucose at 60 min were performed for the data as a group and each patient as an individual over the time intervals 4.0–1.5 yr and 1.5–0 yr before diabetes. Positive and negative predictive values were assessed with 2 × 2 tables.

RESULTS

Fasting glucose versus years to type I diabetes. For the five intensively studied patients, the plot of 83 fasting plasma glucose determinations versus years to type I diabetes was divided with 1.5 yr as a convenient separation point. The regression lines for the two resulting time periods, 4.0–1.5 yr before overt diabetes and 1.5–0 yr before diabetes, are shown in Fig. 1. As seen in the time period 4.0–1.5 yr, there is no significant change in plasma glucose ($r = 0.21$, $P = 0.18$, slope = 2.1 $mg \cdot dl^{-1} \cdot yr^{-1}$). In contrast, the time period from 1.5 yr to diagnosis of overt diabetes shows a progressive rise in fasting glucose ($r = 0.58$, $P < 0.001$, slope = 23.1 $mg \cdot dl^{-1} \cdot yr^{-1}$).

When each patient was plotted individually for fasting glucose versus years to type I diabetes, a similar pattern could be appreciated for the >1.5- and <1.5-yr periods (Table 3). Two patients had few points in the <1.5-yr period ($n = 2$ and $n = 3$); therefore, statistical tests were not applicable although they showed a similar trend.

Glucose at 60 min on IVGTT versus years to type I diabetes. For the five intensively studied patients, plots of glucose at 60 min on IVGTT for the intervals of <1.5 yr to overt diabetes and 4.0–1.5 yr before diabetes are shown in Fig. 2. A similar trend can be seen in the two plots when compared with the plots of fasting glucose versus years to type I diabetes. Linear regression of values <1.5 yr gave an $r = 0.46$, $P = 0.01$, and slope = 47.5 $mg \cdot dl^{-1} \cdot yr^{-1}$. As before, a lack of significant correlation and minimal slope ($r = 0.08$, $P = 0.72$, slope = 2.9 $mg \cdot dl^{-1} \cdot yr^{-1}$) was observed in the period of 4.0–1.5 yr.

Finally, for the five intensively studied patients, linear

TABLE 1
Attributes of 5 prediabetic patients at time of enrollment

Patient	Initial age (yr)	Sex	Relation to proband	Initial HbA_{1c} (%)*	Initial fasting glucose	Initial OGTT (min)	
						60	120
1 (16.13)	66	F	Parent	5.5	88	154	138
2 (20.23)	8	M	Offspring	5.2	81	68	98
3 (4.7)	25	M	Sibling	5.1	81	169	117
4 (11.7)	8	F	Sibling	5.3	70		
5 (20.23)	14	M	Monozygotic twin		76	101	101

Numbers in parentheses refer to patient code on top left-hand corner of graphs in Fig. 5. OGTT, oral glucose tolerance test.
*HbA_{1c}, normal 4–6%.

TABLE 2
Attributes of second prediabetic group

Patient	Initial age (yr)	Sex	Relation to proband	Initial HbA_{1c} (%)*	Initial fasting glucose	Initial OGTT (min)	
						60	120
1 (13.2)	19	F	Sibling		99	206	115
2 (3.2)	15	M	Sibling	5.4	84		
3 (3.4)	7	F	Sibling		88		
4 (18.7)	10	F	Monozygotic twin	4.7	83	119	89
5 (4.7)	58	F	Parent	5.8	95	153	135
6 (3.15)	9	F	Sibling	5.1	88		
7 (2.12)	2.6	F	Sibling		83		
8 (18.12)	35	F	Monozygotic twin		89		
9 (3.13)	22	F	Monozygotic twin		85	218	214
10 (4.13)	39	M	Parent		135		
11 (10.15)	10	M	Sibling		76		
12 (10.12)	9	M	Sibling		118		
13 (11.2)	5	F	Sibling	5.5	68		
14 (3.42)	16	M	Sibling	4.6	86		

Numbers in parentheses refer to patient code on top left-hand corner of graphs in Fig. 5. OGTT, oral glucose tolerance test.
*HbA_{1c}, normal 4–6%.

regression analysis of stimulated insulin versus years to type I diabetes (Fig. 3) gives a highly significant correlation ($r = 0.67$, $P < 0.001$). The slope of the regression line is $-7.5\ \mu U \cdot ml^{-1} \cdot yr^{-1}$.

Positive and negative predictive values. We sought to define values of fasting glucose, glucose at 60 min, and stimulated insulin that predict the likelihood of a prediabetic patient with such a value to be inside or outside the 1.5-yr period to diabetes. To do this, we constructed 2 × 2 tables for fasting glucose, glucose at 60 min, and stimulated insulin and calculated positive and negative predictive values. The following is an example of how this was done: what are the positive and negative predictive values for a patient with fasting glucose >108 or <108 mg/dl developing overt diabetes within 1.5 yr? As shown in Table 4, true-positive values will be >108 mg/dl and occur within 1.5 yr of overt diabetes, whereas true-negative values will be <108 mg/dl and fall outside the 1.5-yr period. Our data had 11 true-positive values, 0 false-positive values, 44 true-negative values, and 28 false-negative values. Hence, the positive predictive value with a fasting glucose >108 mg/dl that predicts a prediabetic patient is within 1.5 yr of diabetes is 100% (11 of 11 values). Likewise, the negative pre-

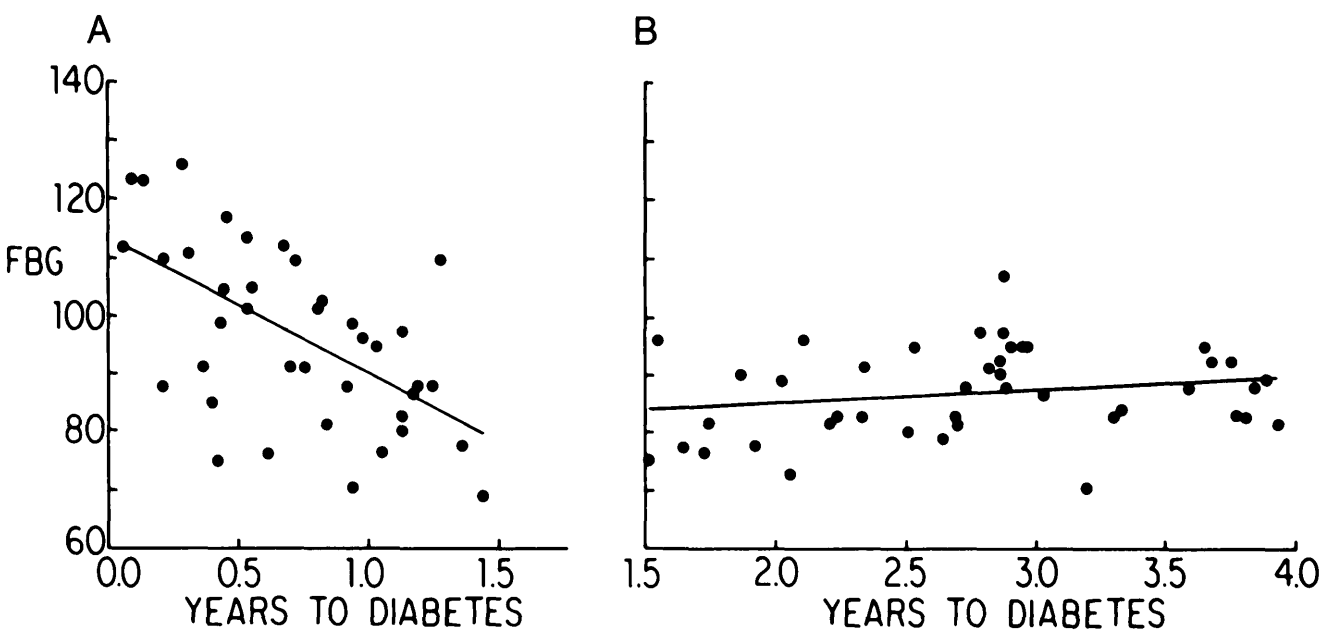

FIG. 1. Fasting plasma glucose (milligrams per deciliter) versus years to onset of diabetes mellitus. *A*: 1.5–0 yr before overt diabetes ($P < 0.001$, $r = 0.58$). *B*: 4.0–1.5 yr before overt diabetes (NS, $r = 0.21$).

TABLE 3
Linear regression analysis of individual fasting glucose data from 5 intensively studied prediabetic patients

	1.5–0 yr					4.0–1.5 yr			
Patient	Tests (*n*)	*r*	*P*	Slope (mg · dl^{-1} · yr^{-1})	Patient	Tests (*n*)	*r*	*P*	Slope (mg · dl^{-1} · yr^{-1})
1	3			12.9	1	9	0.54	0.13	7.2
2	13	0.71	0.006	18.9	2	7	0.43	0.33	−9.8
3	13	0.85	<0.001	30.9	3	19	0.48	0.04	5.0
4	8	0.63	0.09	35.0	4	4	0.21	0.79	−4.6
5	2			46.1	5	5	0.07	0.91	−0.6

Slopes of linear regression lines reflect rise in fasting glucose in milligrams per deciliter per year. Note that slopes for each individual are much greater in 1.5- to 0-yr period than 4.0- to 1.5-yr period.

dictive value that a prediabetic patient with a fasting glucose <108 mg/dl is outside the 1.5-yr period is 61% (44 of 72 values).

We determined that 108 mg/dl gave the best positive predictive value by testing values of fasting glucose between 80 and 110 mg/dl at 2-mg/dl increments for 1.5, 1.0, and 0.5 yr before overt diabetes. For glucose at 60 min, values >120, >140, >160, and >180 mg/dl were used. The values used for stimulated insulin were <24 (1st percentile), <14, and <4 μU/ml. A negative predictive value of 100% (10 of 10 values) was obtained for stimulated insulin >24 μU/ml for a prediabetic first-phase insulin to be >1.0 yr before overt diabetes and 90% (9 of 10 values) at >1.5 yr. Glucose at 60 min at any cutoff point was neither as good a positive predictor of time to overt diabetes as fasting plasma glucose nor as good a negative predictor as stimulated insulin.

We tested the positive and negative predictive values derived from the initial five prediabetic patients (fasting glucose >108 mg/dl and stimulated insulin >24 μU/ml) in a second group of prediabetic patients who were not initially selected because each patient had a limited number of fasting glucose determinations and IVGTTs. The positive predictive value for fasting glucose >108 mg/dl was again 100% (5 of 5 values) at <1.5 yr. The negative predictive value of stimulated insulin >24 μU/ml was 63% (5 of 8 values) at >1.5 yr and 89% (6 of 7 values) at >1 yr. The three values of stimulated insulin >24 μU/ml within 1.5 yr of diabetes were all in younger patients (<18 yr of age).

Figure 4 plots fasting glucose, glucose at 60 min on IVGTT, and stimulated insulin versus age in years for two patients with stimulated insulin above the 1st percentile before onset of overt hyperglycemia (see also patients 11.2 and 3.42 of Fig. 5). The stimulated insulin value was normal (14th percentile) 5 mo before onset of hyperglycemia in Fig. 4*A* and normal (54th percentile) 11 mo before onset of hyperglycemia in Fig. 4*B*. In

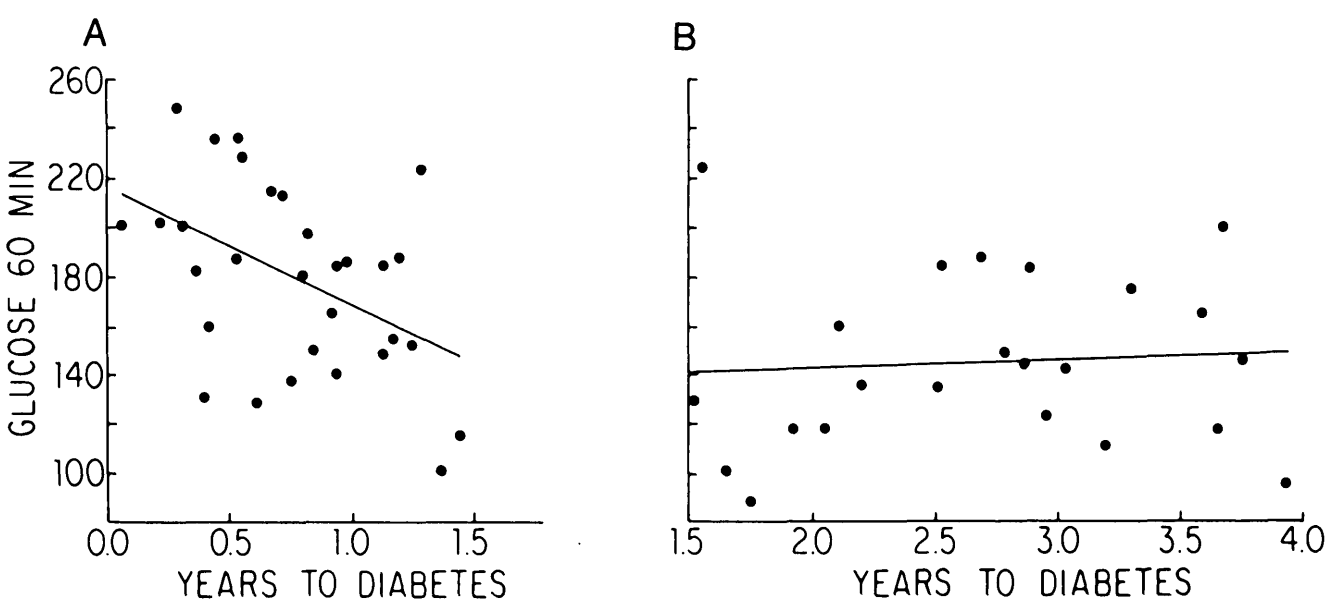

FIG. 2. Glucose at 60 min on intravenous glucose tolerance test (milligrams per deciliter) versus years to onset of diabetes mellitus. *A*: 1.5–0 yr before overt diabetes (P = 0.01, r = 0.46). *B*: 4.0–1.5 yr before overt diabetes (NS, r = 0.08).

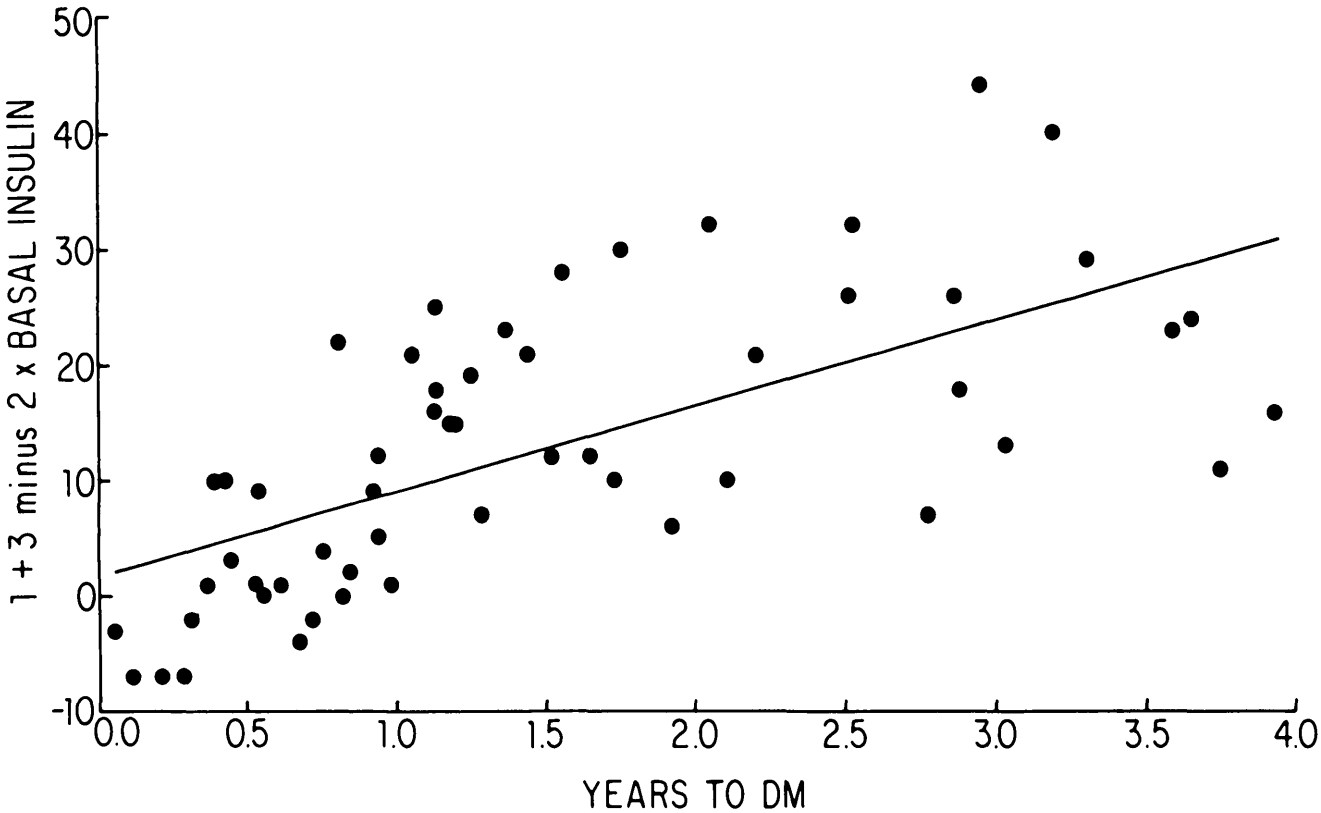

FIG. 3. One plus three minute minus (2 × basal) insulin (stimulated) versus years to onset of diabetes mellitus (DM) for 4.0–0 yr ($P < 0.001$, $r = 0.67$).

addition, patient 11.2 showed a progressive rise in fasting glucose beginning 8 mo before overt diabetes with a fasting glucose >120 mg/dl and an abnormal oral glucose tolerance test 3 mo before diagnosis of diabetes. Thus, stimulated insulin failed to predict lack of progression to overt diabetes in these patients. To date, 2 of 19 patients overall (11%) and 2 of 9 children <18 yr of age (22%) have developed diabetes without documented loss of stimulated insulin secretion in the 1.5 yr before diabetes. Whether this observation is due to heterogeneity in the way patients develop diabetes or a lack of IVGTT measurements during a short but critical time interval before overt hyperglycemia remains to be determined.

TABLE 4
Calculation of positive and negative predictive values

	1.5–0 yr	4–1.5 yr
>108 mg/dl	A	B
	11	0
	True positive	False positive
<108 mg/dl	C	D
	28	44
	False negative	True negative

2 × 2 table. Positive predictive value, A/A + B = 11 of 11 = 100%; negative predictive value, D/C + D = 44 of 72 = 61%.

Figure 5 plots the fasting glucose of all ICA$^+$ relatives who have progressed to diabetes and for contrast Fig. 6 plots the ICA$^+$ relatives who currently do not have diabetes. As expected, many but not all prediabetic patients had fasting glucose >108 mg/dl before the development of severe hyperglycemia. Only 2 of 16 relatives who did not progress to diabetes have a glucose >108 mg/dl and neither of these individuals had >1 yr of follow-up since measurement of this glucose. None of the currently nondiabetic relatives have a stimulated insulin <24 μU/ml.

In our cohort, 83% (10 of 12) of patients with a fasting glucose determination >108 mg/dl have diabetes at current follow-up, whereas only 33% (9 of 23) of patients with all fasting glucose measurements <108 mg/dl have diabetes to date ($P < 0.02$).

DISCUSSION

Results of this study can be summarized in four statements: *1*) there is a progressive rise in fasting glucose beginning ~1.5 yr before the onset of hyperglycemia; *2*) fasting plasma glucose >108 mg/dl is a strong positive predictor for progression to overt diabetes within 1.5 yr; *3*) stimulated insulin >24 μU/ml is a strong negative predictor for lack of progression to overt diabetes over a 1-yr period; and *4*)

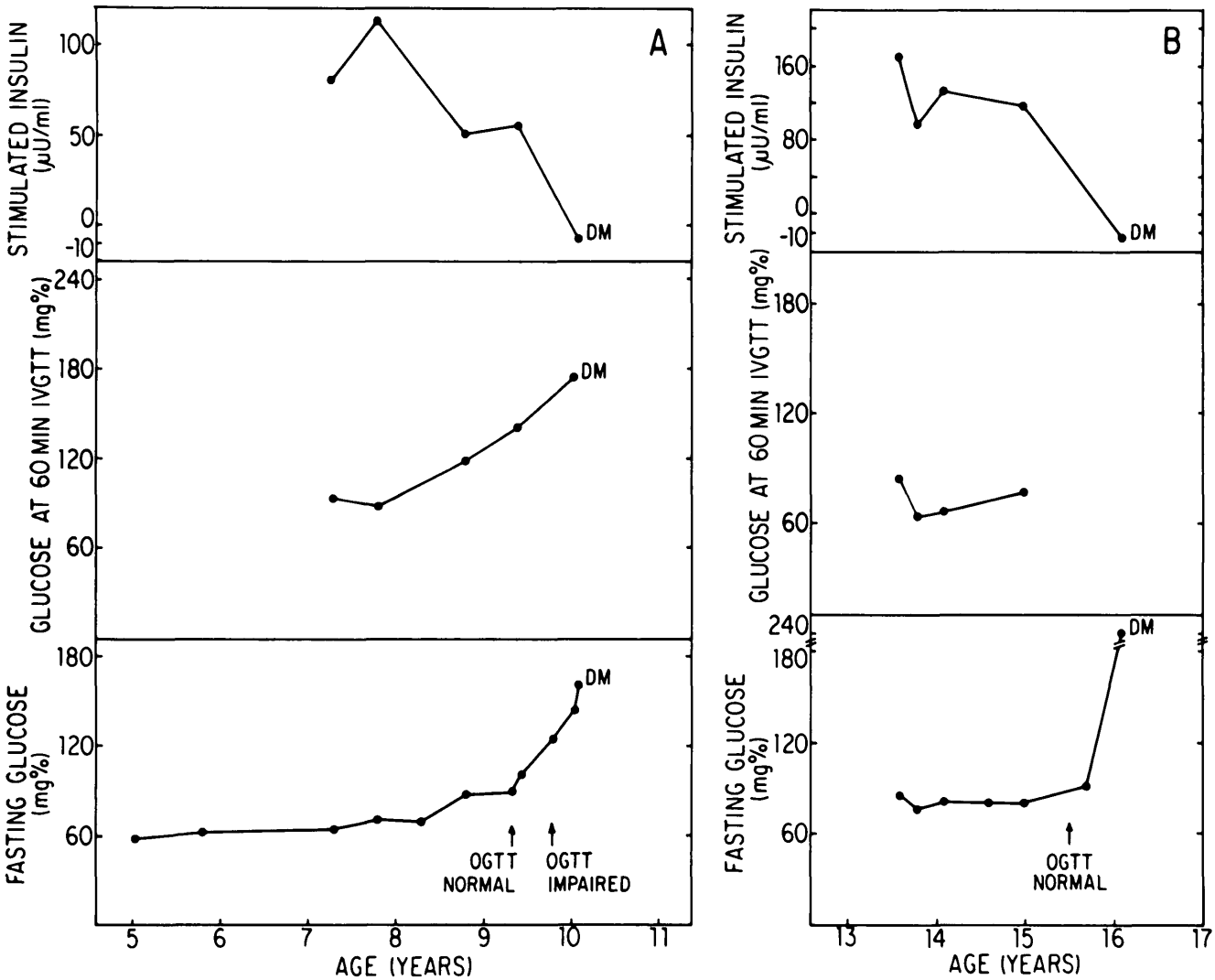

FIG. 4. Stimulated insulin (*upper panel*), glucose at 60 min on intravenous glucose tolerance test (IVGTT) (*middle panel*), and fasting plasma glucose (*lower panel*) versus age in years plotted for two patients (*A*, patient 11.2; *B*, patient 3.42) who did not lose stimulated insulin secretion before overt hyperglycemia. DM, time of diagnosis of diabetes. Oral glucose tolerance tests indicate normal and impaired according to National Diabetes Data Group criteria.

there is a significant subset of patients who develop diabetes without observed loss of stimulated insulin secretion within 1 yr of onset of hyperglycemia.

Note that the development of type I diabetes in ICA$^+$ relatives appears to be a chronic metabolic process with a progressive rise of glucose in the last 1.5 yr. The ability to predict onset of clinical diabetes in an ICA$^+$ relative of a type I diabetic patient may therefore be aided by routine fasting glucose measurement. The combination of fasting plasma glucose and first-phase insulin release can define for most prediabetic patients their likelihood of progressing to overt diabetes over a 1.5-yr period.

A report from Tarn et al. (9) on the Barts-Windsor family study with fewer glucose determinations per individual looked at random blood glucose concentration and oral glucose tolerance testing in 13 first-degree relatives of children with type I diabetes. All patients had HLA-DR4, DR3, or both, and all but two were ICA$^+$. Retrospectively, most individuals met diabetic criteria at initial study, but were not treated with insulin as per the design of the study until overt diabetes was diagnosed. Of the 13 patients who progressed to insulin treatment, 10 showed progressive or intermittent hyperglycemia over many months and the others had nonspecific symptoms suggestive of hyperglycemia over a long period of time despite the failure to document overt hyperglycemia. These results argue for progressive loss of glucose homeostasis over months before the institution of insulin treatment.

Chase et al. (10) studied 66 ICA$^+$ first-degree relatives with IVGTT. Approximately 50% of these patients were <18 yr of age (34 of 66) and 38% (13 of 34) had a first-phase insulin release (1-min + 3-min insulin) <67 μU/ml. In those >18 yr of age (32 of 66), only 16% (5 of 32) had a first-phase insulin release <67 μU/ml. During a 12-mo follow-up period, 7 of 13 patients in the

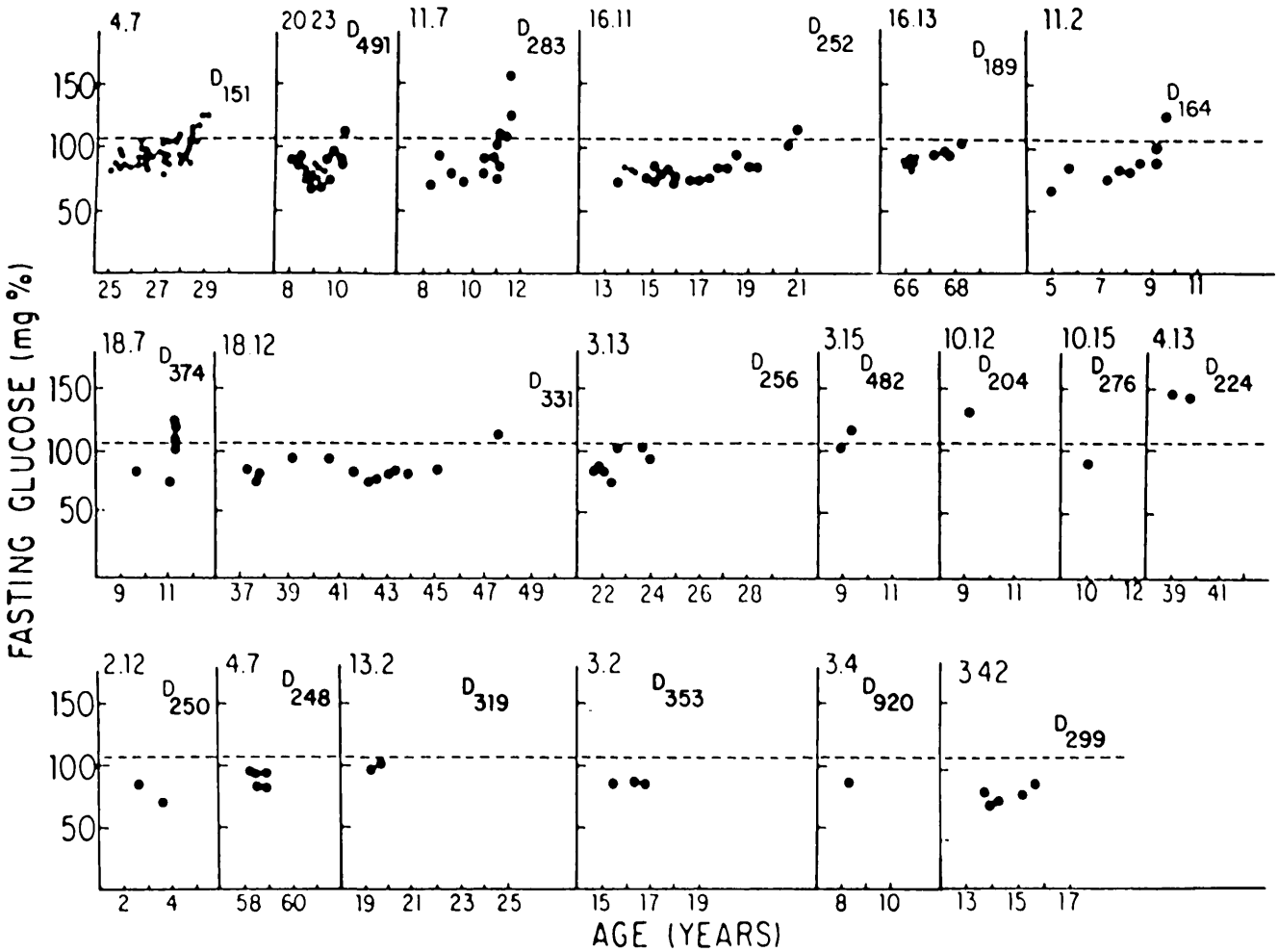

FIG. 5. Fasting plasma glucose versus age in years for 19 patients who developed overt diabetes. Number in *upper left-hand corner* on each plot gives patient code. D, diagnosis of overt diabetes with number giving value of diagnostic glucose. *Dotted line* gives 108-mg/dl cutoff point.

<18 yr of age group developed overt diabetes, whereas 0 of 5 patients in the >18 yr of age group did. In the <18 yr of age group the probability of developing type I diabetes within 12 mo, with 95% confidence, was 59–100% when the first-phase insulin release was <25 μU/ml. Note that 4 of 7 children already had elevated HbA_{1c} at the time of initial IVGTT.

Obvious questions raised by our study are what preserves glucose homeostatic function during the 2.5-yr period (4.0–1.5 yr) when stimulated insulin secretion (1-min + 3-min insulin − 2 × basal insulin) is often below the 5th percentile (48 μU/ml) of the nondiabetic population and furthermore, what causes deterioration in this function during the 1.5- to 0-yr period? Also, what precipitates acute deterioration in glucose homeostasis resulting in glucose frequently >200 mg/dl at the time of diagnosis of diabetes? Finally and most important, is there a subset of patients whose progression to diabetes will be missed unless monthly fasting glucose and IVGTT measurements are performed?

In conclusion, our study reveals progressive loss of glucose homeostasis in the last 1.5 yr before overt diabetes in many ICA^+ first-degree relatives of type I diabetic patients. This information combined with the negative predictive value of stimulated insulin should aid in assigning the risk of imminent diabetes in an ICA^+ relative. For several children, fasting glucose can be normal even within 3 mo of the onset of overt diabetes, and thus a lack of fasting glucose >108 mg/dl does not rule out the imminent development of overt disease. We suspect that some of our younger relatives have a rapid course of β-cell destruction and monthly measurements may be necessary to monitor their course.

ACKNOWLEDGMENTS

This work was supported by National Institutes of Health (NIH) Grants DK-33790, DK-39233, and DK-32083; NIH National Institute of Diabetes and Digestive and Kidney Diseases Training Grant DK-07260; and Diabetes Endocrine Research Center Grant IP30-DK-36837, with core

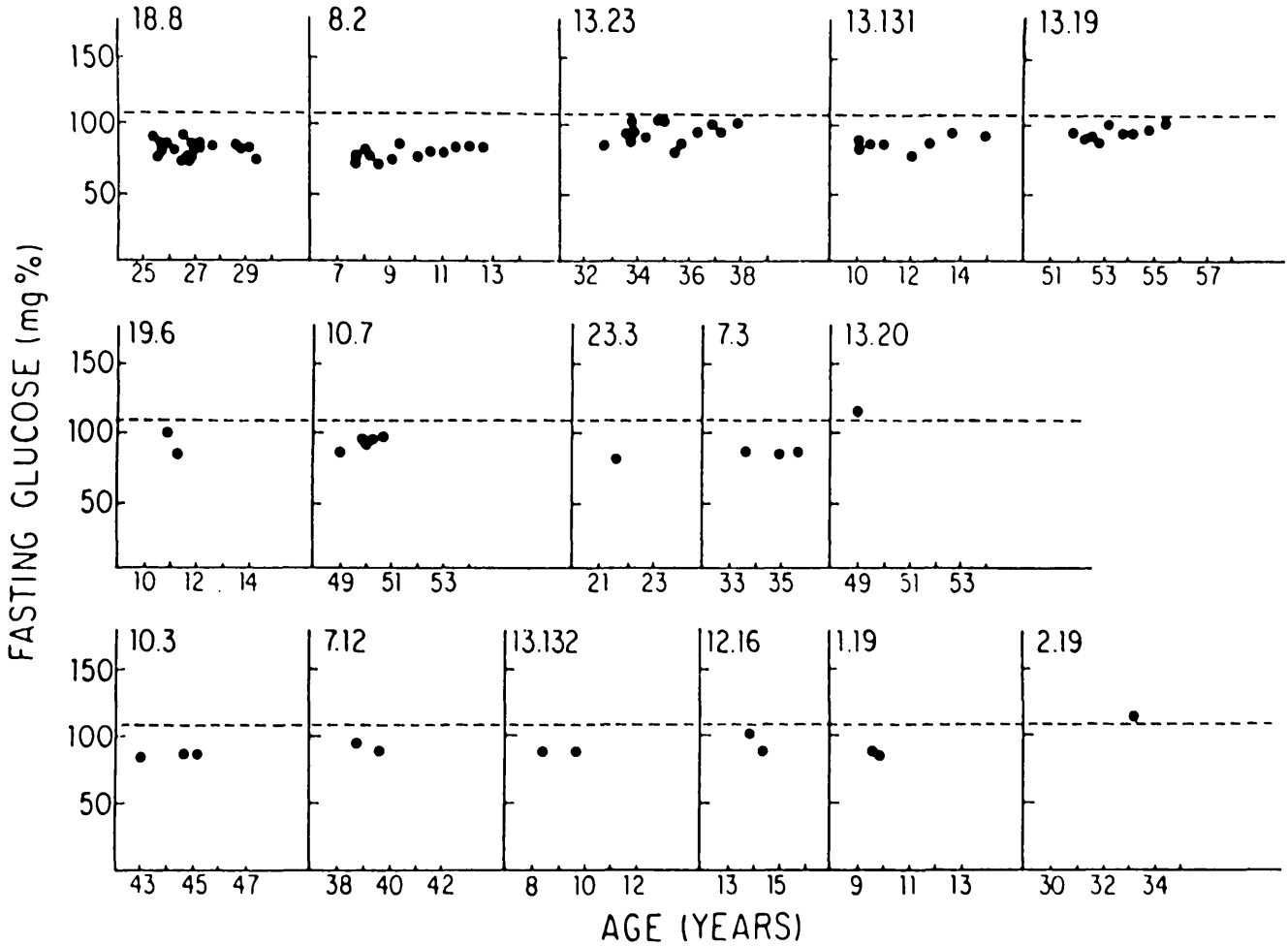

FIG. 6. Fasting plasma glucose versus age for islet cell–antibody–positive relatives who have not progressed to overt diabetes.

facilities including radioligand and clinical research, the Massachusetts Lions Eye Research Fund and the Dana Foundation. Clinical Research Center CLINFO (Brigham and Women's Hospital) was used for data analysis.

We acknowledge the technical support of A. Rabizabeh, M. Gringbergs, I. Reske, M. Tautkus, and M. Petruzzelli and the secretarial assistance of P. Cronin-Sevigny. The nursing skill of T.M. Smith is greatly appreciated.

REFERENCES

1. Rossini AA, Mordes JP, Like AA: Immunology of insulin-dependent diabetes mellitus. *Annu Rev Immunol* 3:289–320, 1985
2. Dean BM, Becker F, McNally JM, Tarn AC, Schwartz G, Gale EAM, Bottazzo GF: Insulin autoantibodies in the pre-diabetic period: correlation with islet cell antibodies and development of diabetes. *Diabetologia* 29:339–42, 1986
3. Doberson MJ, Chase HP: Immunologic aspects of type I diabetes. *Pediatrician* 12:173–78, 1986
4. Pozzilli P, Sensi M, Sakkai LA, Tarn A, Zaccarini O, Bottazzo GF: Prospective study of lymphocyte subsets in subjects genetically susceptible to type I (insulin-dependent) diabetes. *Diabetologia* 27:132–35, 1984
5. Srikanta S, Ganda OP, Gleason RE, Jackson RA, Soeldner JS, Eisenbarth GS: Pre-type I diabetes: linear loss of beta cell response to intravenous glucose. *Diabetes* 33:717–20, 1984
6. Riley W, Maclaren N, Spillar R, Krischer J, Silverstein J, Malone J, Schwartz S, MacMillan D, Rotter J: Predictive value of ICA for IDD and insulinopenia to IV glucose (Abstract). *Diabetes* 37 (Issue 5 Suppl.):5A, 1988
7. Gale EAM, Bottazzo GF: Can we predict type I (insulin-dependent) diabetes? In *World Book of Diabetes in Practice*. Vol. 2. Krall L, Ed. New York, Elsevier, 1986, p. 25–29
8. Soeldner JS: The intravenous glucose tolerance test. In *Diabetes Mellitus: Diagnosis and Treatment*. Vol. 3. Fajans SS, Sussman KE, Eds. New York, Am. Diabetes Assoc., 1971, p. 107–13
9. Tarn AC, Smith CP, Spenser KM, Bottazzo GF, Gale EAM: Type I (insulin-dependent) diabetes: a disease of slow clinical onset? *Br Med J* 294:342–45, 1987
10. Chase PH, Voss MA, Butler-Simon N, Hoops S, O'Brien D, Doberson MJ: Diagnosis of pre-type I diabetes. *J Pediatr* 111:807–12, 1987