Pre-Type I Diabetes

Linear Loss of Beta Cell Response to Intravenous Glucose

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SUMMARY

Twenty-one intravenous (i.v.) glucose tolerance tests were performed on nine subjects before the onset of overt type I diabetes mellitus. Islet cell antibodies (6 of 9 subjects) and elevated levels of Ia-positive T-lymphocytes (3 of 3 subjects studied) were detected during the prediabetic period. Elevations of fasting blood glucose and peak glucose during oral glucose tolerance tests were not observed until the year before onset of clinically overt diabetes. During the prediabetic period, there was a progressive loss of early-phase insulin release to i.v. glucose (rate of decline, 20–40 μU/ml insulin release/yr; correlation coefficient, 0.9). DIABETES *33*:717–720, August 1984.

An increasing body of evidence suggests that type I diabetes mellitus is a "slow" autoimmune disease. Recent reports indicate that the immunologic abnormalities of type I diabetes (islet cell antibodies and activated T-cells) may precede the overt development of insulin-dependent diabetes mellitus by several years.[1–8] Moreover, we have recently discovered a chronic progressive loss of beta cell function temporally associated with the presence of islet cell antibodies in a prospective 21-yr study of monozygotic twins initially discordant for type I diabetes mellitus.[7,8] In particular, during the "prediabetic" phase, these twins demonstrated a progressive decline in the first-phase insulin response to intravenous (i.v.) glucose. In this communication, we present our findings and regression analysis on 9 individuals studied to date (including 5 twins), in whom we had the opportunity to study i.v. glucose tolerance test responses before diagnosis of overt type I diabetes.

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MATERIALS AND METHODS

Nine subjects in whom i.v. glucose tolerance tests (IVGTTs) were performed before diagnosis of overt insulin-dependent (type I) diabetes were characterized as follows (Table 1): (1) five monozygotic twins initially discordant for type I diabetes mellitus had been prospectively followed in the "twin registry" of the Joslin Diabetes Center (among a total of 24 monozygotic twins);[8] (2) one subject was studied because she was a first-degree relative in a diabetes-multiplex family (3 of her siblings and her aunt have type I diabetes); and (3) three subjects presented with a history of transient glucosuria with normal (1 subject) or impaired glucose tolerance (2 subjects) at the time of initial evaluation, and subsequently developed overt diabetes.

An additional 15 monozygotic twins discordant for type I diabetes mellitus (14 immunologically normal; one with elevated Ia+ T-cells) have also been followed for up to 21 yr with serial IVGTTs. More than 200 normal controls (ages 8–77 yr) have been studied for insulin response to i.v. glucose during the same period (many with multiple IVGTTs). Distribution of early peak insulin response (sum of 1- plus 3-min values) during 407 IVGTTs in these normal controls is as follows: first percentile less than 46 μU/ml; fifth percentile less than 67 μU/ml; tenth percentile less than 81 μU/ml; fiftieth percentile less than 169 μU/ml.

IVGTTs were performed by infusing dextrose (0.5 g/kg body wt) over a 2–4-min period. For oral glucose tolerance tests (OGTTs), 100 g of glucose was administered. Whole venous blood glucose was measured by Technicon Auto-Analyzer (Technicon Instruments Corp., Tarrytown, New York).[9] Serum immunoreactive insulin was measured by a double-antibody technique.[10] Islet cell antibodies were measured by indirect immunofluorescence on frozen sections of human pancreas.[11] Ia-positive T-cells were measured on individuals studied in the past 1 yr using monoclonal antibody L243.[5]

RESULTS

Figure 1 presents plots of the relationship of fasting blood glucose, peak glucose during OGTT, and peak insulin (sum

TABLE 1
Characterization of subjects studied

Subject		Sex	Duration ICA before DM (yr)	Ia+ T-cells (normal < 5%)	Age at onset of overt DM (yr)	% Ideal body weight
Monozygotic twins						
1	16.11	M	>8	ND*	21	95
2	18.12	M	5	ND	48	90
3	3.13	F	>7	ND	28	78
4	3.2	F	—	ND	14	88
5	18.7	F	>1.5	13%	11	91
First-degree relative						
6	13.2	F	>3	ND	22	107
History of transient glucosuria						
7	20.6	M	>4	ND	27	113
8	3.19	F	—	7%	10	91
9	11.2	F	—	8%	12	106

*ND, not determined.

of 1- and 3-min values) response to i.v. glucose to years before development of overt diabetes. Fasting blood glucose was within the normal range until a year before the onset of overt diabetes (Figure 1, top panel). Similarly, peak glucose on OGTTs did not rise until immediately before the diagnosis of overt diabetes (Figure 1, middle panel). In contrast, there was a steady, progressive decline in peak insulin release to i.v. glucose during the prediabetic phase with an r-value of 0.90 ($P < 0.001$) and a slope of 21 μU/ml/yr decline in insulin release.

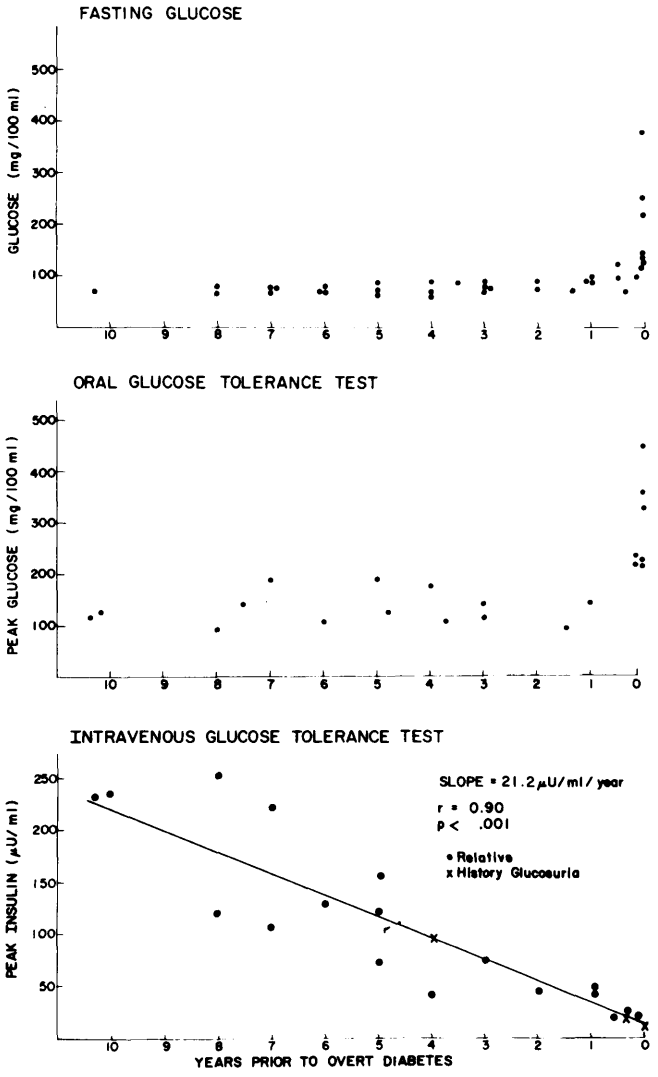

FIGURE 1. Relationship of fasting blood glucose, peak glucose during OGTT, and peak insulin (sum of 1- and 3-min values) response to i.v. glucose to years before diagnosis of overt diabetes (N = 9 subjects).

Figure 2 shows the serial peak insulin responses during IVGTTs in the 9 prospectively studied subjects before the development of overt type I diabetes. There was a progressive decline in the insulin response to low levels during the prediabetic phase in all the subjects studied with repetitive IVGTTs. The rate of decline of early-phase insulin release was 38 ± 8 μU/ml/yr (calculated using a total of 11 data points from 4 patients [#1, 2, 3, and 5] with multiple [2–3] IVGTTs before diabetes). In all but one of these individuals (in that individual, Ia+ T-cells were not studied) islet cell antibodies or Ia-positive T-cells were present before overt diabetes during the progressive loss of insulin release.[7,8] In patient 16.11, antibodies were present for 3 yr while there was stable insulin release before its fall. In patient 18.12, conversion to antibody positivity temporally correlated with decreased insulin release.[7,8]

Figure 3 shows the serial first-phase insulin response to i.v. glucose in 15 islet cell antibody-negative, discordant (nondiabetic) twins (age at the time of initial study, 11–53 yr). With up to 17 yr of follow-up, none of these twins have developed diabetes. One of these twins (○— —○) has shown a steady progressive decline in insulin response and it is interesting to note that Ia+ T-cells were elevated in this twin over the past 1 yr. Ia-positive T-cells have been studied only in the past 1 yr and all other twins studied (10 individuals) in this group have <3% Ia+ T-cells (normal value). In the remaining 14 immunologically normal twins, variation in insulin responses at higher insulin levels is evident, but none of these individuals have progressed below the first percentile for normal controls (i.e., 46 μU/ml), and the two individuals with the lowest insulin release have remained stable for the last 5 and 14 yr, respectively.

DISCUSSION

Longitudinal data on beta cell function during the period preceding the development of overt type I diabetes mellitus

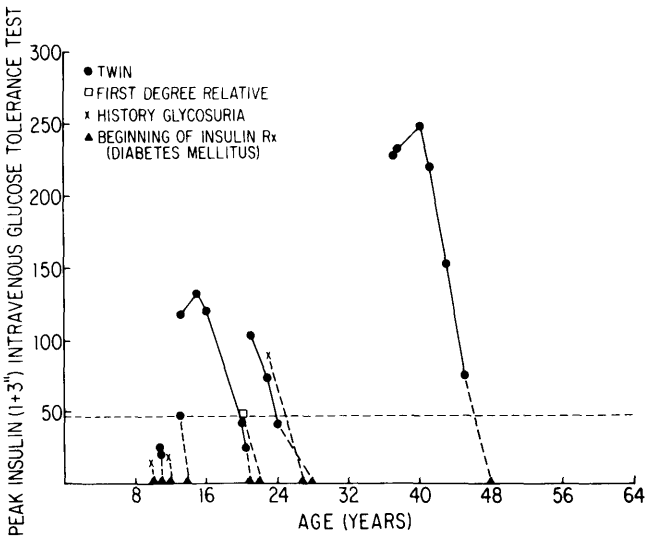

FIGURE 2. Serial peak insulin responses during IVGTTs before the development of overt type I diabetes (DM) (N = 9 subjects). Dashed horizontal line represents the first percentile response for normal controls (46 μU/ml).

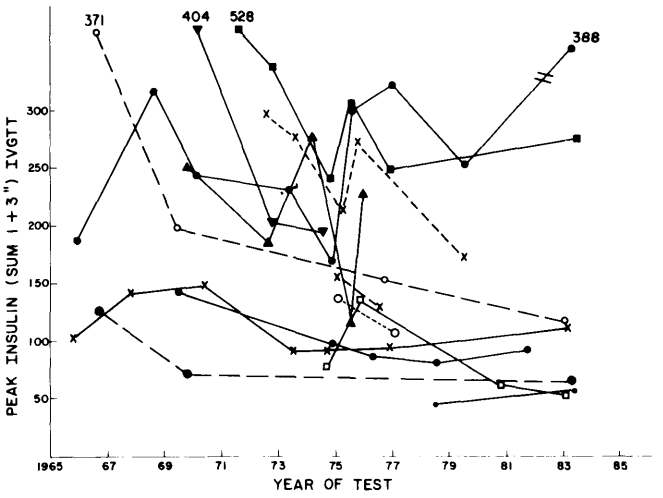

FIGURE 3. Serial peak insulin responses to i.v. glucose in 15 islet cell antibody-negative, discordant (nondiabetic) twins. Ia+ T-cells were elevated only in a nondiabetic twin (○— —○) who also has shown a steady progressive decline in insulin response.

are limited. Cerasi and Luft reported a delayed and decreased insulin response to glucose infusion in five adult monozygotic twins whose twin siblings had diabetes (type unspecified).[12] Irvine et al. found no significant differences between the mean insulin concentrations of islet cell antibody-positive subjects with normal glucose tolerance and controls during OGTTs, but islet cell antibody-positive subjects with impaired glucose tolerance had higher mean basal insulin concentrations and higher mean insulin concentrations than controls at 90, 120, and 150 min, interpreted as delayed insulin release.[3] Tiengo et al. found normal insulin secretion after oral or i.v. glucose administration in 14 subjects with ICA and normal glucose tolerance.[13] On the other hand, Hollander et al. reported an exaggerated acute-phase insulin secretion to i.v. arginine and glucose in HLA-identical siblings of patients with insulin-dependent diabetes compared with controls.[14] None of these studies provide longitudinal evaluation of insulin secretory dynamics or document subsequent progression to overt diabetes.

We have had the opportunity to study IVGTT responses in 9 individuals before the development of overt type I diabetes. Despite the small number of individuals studied to date, all subjects followed a similar course, with a linear loss of insulin release to i.v. glucose giving a correlation coefficient of 0.9 (insulin release versus years before overt diabetes). The rate of decline of early-phase insulin release was approximately 20–40 μU/ml/yr. Elevations in fasting blood glucose and peak glucose during OGTT were not seen until the year before onset of clinically overt diabetes.

Serial evaluation of insulin release to i.v. glucose in immunologically normal, but genetically predisposed, subjects (i.e., monozygotic twins discordant for type I diabetes) revealed considerable variation (Figure 3) in insulin responses, particularly at higher levels of serum insulin. In contrast to the immunologically abnormal subjects, none of these twins showed a steady progressive decline in first-phase insulin release below the first percentile for normal controls (46 μU/ml). In the absence of islet cell antibodies and activated T-cells, insulin release to i.v. glucose has been stable in the two twins with lowest insulin responses over the last 5 and 14 yr, respectively.

It should be noted that these prospective studies were initiated without a knowledge of which endocrinologic parameter would be most sensitive in detecting changes before overt diabetes develops.[15] In retrospect, we regret the absence of more frequent measurement of response to i.v. glucose. Thus, our data are limited and we cannot exclude that insulin secretory capacity may decline in some individuals in a stepwise fashion or that there are periods of recovery with an overall downward trend.

If first-phase insulin release decreases in a linear manner in a larger group of immunologically abnormal subjects, it may be possible to predict when a genetically predisposed relative of a type I diabetic proband will develop overt diabetes. Serial determination of insulin release to i.v. glucose might also provide a useful parameter to evaluate the influence of immunotherapy initiated before the appearance of overt diabetes.

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