β-Cell Function and Insulin Sensitivity in Nondiabetic HLA-Identical Siblings of Insulin-Dependent Diabetics

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SUMMARY

Insulin secretion and insulin sensitivity were compared in 12 HLA-identical siblings of insulin-dependent diabetics and nondiabetic controls. Only the maximum acute insulin response to intravenous arginine was lower in the siblings than in the matched controls ($P <$ .05); other measures of insulin secretion, including the acute insulin response to glucose or arginine, the second-phase insulin response to glucose, and the slope of glucose potentiation, were not significantly different. Insulin sensitivity, derived from an intravenous glucose tolerance test with a minimal-modeling technique, was lower in the siblings ($P <$ .01). In a large group of nondiabetic controls of various adiposity, insulin secretion and insulin sensitivity were inversely related. In view of the difference in insulin sensitivity between siblings and matched controls, a direct comparison of β-cell function tests may be inappropriate, and the measures of insulin secretion were compared with those of nondiabetics when adjusted for differences in insulin sensitivity. This analysis revealed that all measures of insulin secretion were significantly lower in the siblings. We conclude that HLA-identical siblings of insulin-dependent diabetics show evidence of both insulin resistance and impaired β-cell function and that analysis of β-cell function in relation to insulin sensitivity shows a greater frequency of β-cell secretory abnormalities than previously appreciated. *Diabetes* 36:829–37, 1987

The development of insulin-dependent diabetes mellitus (IDDM) is currently thought to occur in genetically susceptible individuals by immune-mediated β-cell destruction (1). The presence of immunological markers, e.g., islet cell antibodies, before the onset of hyperglycemia suggests that β-cell destruction occurs over a period of months or years, eventually leading to sufficient insulin deficiency to result in hyperglycemia (2).

The genetic susceptibility for the development of IDDM is strongly associated with particular antigens within the major histocompatibility complex or HLA system (3). It has been estimated that siblings of an IDDM patient have an ~27 times increased risk of developing IDDM by the age of 16 (3,4) and that this risk increases to ~90 times if the siblings have HLA antigens identical to those of their diabetic sibling (4).

Attempts to quantify β-cell dysfunction in nondiabetic high-risk subjects with secretagogues, e.g., glucose, arginine, and glucagon, have yielded apparently contradictory results. Oral glucose tolerance tests in identical twins and HLA-identical siblings of IDDM patients have shown both hyperinsulinemic (5–7) and hypoinsulinemic (8) responses. Recent reports from the Joslin Clinic have indicated that the insulin response to oral glucose may be relatively preserved despite marked diminution in the acute insulin response (AIR) to intravenous glucose (9,10), but this response can also be very variable (11). In a previous study, we demonstrated that HLA-identical siblings of an IDDM patient had an exaggerated AIR when compared with matched controls (12).

Some of the variation of insulin responses in previous studies could be due to the effect of insulin sensitivity on islet cell function. Individuals with in vivo states of insulin resistance, e.g., obesity, have absolute hyperinsulinemia (13). The insulin response to oral glucose correlates directly with the degree of insulin sensitivity as estimated by the euglycemic-hyperinsulinemic clamp technique (14), and induction of insulin resistance by the administration of corticosteroids increases β-cell responsiveness (15). Thus, insulin sensitivity needs to be considered when β-cell function tests are compared.

We have recently shown that a group of 12 HLA-identical siblings of IDDM patients were insulin resistant compared

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with a matched group of nondiabetic controls (16). This report describes insulin secretion in the same 12 HLA-identical siblings, assessed both in response to intravenous glucose directly and to the potentiating effects of plasma glucose on the insulin response to arginine. The aim was to determine whether insulin secretion in the siblings was appropriate for their degree of insulin sensitivity.

MATERIALS AND METHODS

Twelve HLA-identical siblings were studied. Subjects were recruited from families in which at least one sibling had IDDM as defined by the National Diabetes Data Group (17). All available family members had been typed for the presence of HLA-A, -B, and -DR antigens by standard techniques (18,19). The HLA-identical siblings have been discordant from their diabetic siblings for at least 16 yr, with a mean of 19 yr. All are Caucasian, and at the time of testing, none had detectable islet cell antibodies. Each sibling was pair matched with a control of the same sex, age (±5 yr), and ideal body weight (±10% of study subject's percent of ideal body weight; Metropolitan Life Insurance tables, 1959). None of the control subjects' parents or siblings had a history of diabetes. None of the subjects, either siblings or controls, was receiving medication at the time of the studies.

The insulin sensitivity index of the matched controls was mostly in the middle of the normal range; therefore, to evaluate insulin secretion in relation to insulin sensitivity, it was necessary to include a larger group of controls with a wider range of sensitivity, especially with values at the lower range. Thus, nine additional controls were included, several of whom by necessity were obese, with a mean ideal body weight of 142% (range 102–211). They had a mean age of 31 yr (range 22–41), and all were women.

Experimental protocol. All subjects were studied as outpatients on an ad libitum diet that was designed to include at least 300 g carbohydrate. The studies were approved by the University of Washington Human Subjects Committee, and written informed consent was obtained. Every subject underwent two studies, each of which commenced at 0800 h after a 12-h fast. Intravenous cannulas were inserted into a peripheral forearm vein of each arm under local anesthesia. The hand and wrist of one arm were placed in a wooden box thermostatically heated to maintain a temperature of 60°C. This cannula was designed to arterialize the venous blood (20). The other cannula was used for the infusion of glucose and arginine. Both cannulas were kept patent by a slow infusion of 0.9% NaCl. The two studies were performed in random order and separated by at least 1 wk.

Intravenous glucose tolerance test (IVGTT). Four-milliliter blood samples were anticoagulated with EDTA and used for the assay of plasma glucose and insulin. Samples were obtained at −20, −15, −10, and −5 min before glucose injection. Three-tenths gram per kilogram body weight of 50% α-D-glucose was given as a bolus over 30 s commencing at time 0. Further blood samples were obtained at 2, 3, 4, 5, 6, 8, 10, 12, 14, 16, 19, 22, 25, 30, 40, 50, 60, 70, 80, 90, 100, 120, 140, 160, and 180 min after the glucose injection. Data from the IVGTT were used to derive the index of insulin sensitivity and to measure the acute and second-phase responses of insulin secretion.

Arginine stimulation. Insulin secretory responses to intravenous arginine were measured at three different plasma glucose levels. For each response, two prestimulus blood samples of 4 ml were obtained 5 min and immediately before each dose of arginine. A maximally stimulating dose of 5 g of 10% arginine hydrochloride was administered intravenously over 30 s, the end of which was designated as time 0 (21). Blood samples for the measurement of the insulin response were obtained 2, 3, 4, and 5 min after arginine administration. After the 5-min sample was obtained, a variable-rate infusion of 10% α-D-glucose was delivered by a peristaltic pump (Polystaltic, Haake Buchler, Saddle Brook, NJ) to raise the plasma glucose to ~230 mg/dl and maintain it at that level. One-milliliter blood samples were obtained every 5 min for bedside measurement of plasma glucose by a portable glucose analyzer (Beckman, Palo Alto, CA), and the glucose infusion rate was adjusted according to a previously described algorithm (22). Thirty minutes after commencing this hyperglycemic clamp, a second arginine pulse was given, and the insulin response was measured as before. To minimize the possibility of a priming effect of prior hyperglycemia, a 150-min waiting period with no glucose infusion followed the second arginine pulse. Then the acute arginine-induced insulin response was measured at the same plasma glucose concentration as the fasting level. The variable-rate glucose infusion was then used to raise the plasma glucose to ~600 mg/dl and maintain it at that level. Thirty minutes after commencing this hyperglycemic clamp, another arginine pulse was administered, and the insulin response was measured. We have previously shown that the maximal hyperglycemic potentiation of the AIR to arginine occurs in both normal controls and non-insulin-dependent diabetics at a plasma glucose concentration of ~460 mg/dl (23). The insulin response measured at or above this glucose concentration is termed the AIR_{max} and is a measure of the maximum glucose-regulated insulin secretory capacity (23).

To exclude a possible effect of catecholamines on islet cell function, two blood samples (2.5 ml each) were drawn before the arginine pulses at fasting glucose concentrations and at the concentration of ~600 mg/dl. These samples were drawn into chilled tubes containing EGTA and glutathione and were assayed for plasma norepinephrine and epinephrine.

Analytical methods. Plasma insulin was assayed by a modification of the double-antibody method of Morgan and Lazarow (24). Plasma glucose was measured on an autoanalyzer by the glucose oxidase method (Technicon, Tarrytown, NY). Plasma epinephrine and norepinephrine levels were measured by single-isotope enzymatic assay (25). F. Bottazzo (Middlesex Hospital, London, UK) tested the serum for islet cell antibodies by indirect immunofluorescence on frozen human pancreas.

Calculations and statistics. Fasting insulin and glucose were calculated as the means of the levels obtained on each of the two days. The AIR to glucose (AIR_{gluc}) was calculated as the incremental area under the insulin curve between 0 and 10 min after the intravenous glucose pulse. The second-phase insulin response to glucose was calculated as the incremental area under the insulin curve from 10 to 60 min after the glucose pulse. Acute insulin secretory response to arginine was measured as the mean of the poststimulus

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TABLE 1
Characteristics

	Age (yr)	IBW (%)	FPG (mg/dl)	Basal insulin (μU/ml)	K_g (%/min)
HLA-identical siblings	25 ± 1.7	102 ± 3.0	91 ± 1.8	11 ± 0.9	1.57 ± 0.1
Matched controls	26 ± 1.5	101 ± 2.4	92 ± 2.0	11 ± 1.4	1.71 ± 0.55

IBW, ideal body weight; FPG, fasting plasma glucose; K_g, glucose disappearance constant. Values are means ± SE.

samples obtained at 2, 3, 4, and 5 min minus the mean of the two prestimulus samples. The AIR to arginine at fasting plasma glucose was termed AIR_{arg}. The AIR to arginine at a plasma glucose level of ~600 mg/dl was termed AIR_{max}. Because the AIR to arginine increases in an approximately linear manner in the plasma glucose range 100–300 mg/dl (23), we calculated the increase in the AIR to arginine obtained during the first hyperglycemic clamp (plasma glucose ~230 mg/dl) above that obtained at fasting plasma glucose divided by the change in plasma glucose $[(AIR_{arg\,(230)} - AIR_{arg\,(fasting)})/\Delta\text{plasma glucose}]$. This is the slope of glucose potentiation (23,26).

The IVGTT was used to estimate the glucose disappearance constant (K_g), calculated as the slope of the decline of plasma glucose (ln) between 10 and 30 min after the glucose injection. The IVGTT was also used to calculate the index of tissue insulin sensitivity (S_I) by the minimal-modeling technique of Bergman et al. (27).

Comparisons between siblings and their pair-matched controls were performed by a paired two-tailed Student's *t* test. The relationship between measures of insulin secretion and insulin sensitivity was examined by linear regression, and comparisons with siblings were made with analysis of covariance. Results are expressed as means ± SE.

RESULTS

Because each pair was carefully matched, there was no significant difference between siblings and controls in either age or percent of ideal body weight. The individual data have been presented previously (16), but the means in the two groups are shown in Table 1. The mean fasting plasma glucose in siblings (91 ± 1.8 mg/dl) was not different from that of their matched controls (92 ± 2.0 mg/dl). The mean fasting plasma insulin concentrations were also identical (siblings 11 ± 0.9; controls 11 ± 1.4 μU/ml). The mean K_g was slightly but insignificantly lower in the siblings than in the controls (1.57 ± 0.1 vs. 1.7 ± 0.55%/min). None of the siblings had a K_g <1.0, which is regarded as the lower limit of normal glucose tolerance (28).

The plasma glucose level achieved during the hypergly-

TABLE 2
Estimates of insulin secretion

	Fasting insulin (μU/ml)	AIR_{gluc} (μU/ml)	Second-phase insulin release (μU/ml)	AIR_{max} (μU/ml)	Glucose potentiation slope	AIR_{arg} (μU/ml)	S_I (× 10^4 min^{-1} · μU^{-1} · ml^{-1})
Siblings							
1	18	180	823	228	0.91	63	4.35
2	11	260	1080	208	0.95	58	3.10
3	9	628	546	288	1.43	44	2.16
4	10	964	644	210	0.73	25	3.03
5	9	345	528	120	0.78	31	3.30
6	6	171	288	115	0.57	22	2.05
7	10	497	1476	187	0.84	34	2.99
8	14	655	1234	320	1.46	63	1.99
9	7	209	767	208	0.67	50	3.71
10	11	472	1020	128	0.78	41	1.93
11	11	374	556	208	0.81	32	3.94
12	14	736	1153	305	1.00	45	3.52
Mean ± SE	11 ± 0.9	458 ± 72	843 ± 101	210 ± 20	0.91 ± 0.08	42 ± 4	3.00 ± 0.24
Controls							
1	17	389	1149	375	1.03	71	2.30
2	8	607	630	253	1.26	55	6.60
3	11	276	785	178	0.47	55	7.30
4	11	211	988	313	0.97	49	5.35
5	5	557	636	188	0.55	29	4.60
6	9	169	438	123	0.51	30	4.76
7	18	385	1350	164	0.46	44	6.40
8	14	289	704	250	1.01	57	8.80
9	8	321	590	315	0.96	56	6.21
10	8	524	894	128	0.68	17	3.71
11	6	323	468	228	0.69	42	5.67
12	20	2329	2205	553	3.12	49	1.80
Mean ± SE	11 ± 1.4	532 ± 168	903 ± 142	256 ± 35	0.98 ± 0.21	46 ± 4	5.29 ± 0.58

AIR_{gluc}, acute insulin response to glucose; AIR_{max}, maximum acute insulin response to arginine; AIR_{arg}, acute insulin response to arginine; S_I, insulin sensitivity.

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cemic clamp was virtually identical in both groups, achieving a mean in the siblings of 229 ± 3 mg/dl and in the controls of 237 ± 4 mg/dl. The mean plasma glucose values during the final glucose infusion were also not different, and AIR_{max} was performed at a plasma glucose of 626 ± 12 mg/dl in the siblings and at 612 ± 12 mg/dl in controls.

The results of the various estimates of insulin secretion for each individual subject and matched controls are given in Table 2. Eight of the siblings had a lower AIR_{max} than their matched controls. The mean level in the siblings (210 ± 20 μU/ml) was significantly ($P < .05$) lower than in the controls (256 ± 35 μU/ml). The mean values for AIR_{gluc} and the second phase of insulin secretion were not significantly different in the siblings and matched controls. Similarly, AIR_{arg} and the slope of glucose potentiation were not different.

The S_I in each sibling and control is also given in Table 2. The mean value in the siblings was significantly lower than in the controls (3.0 ± 0.24 vs. $5.29 \pm 0.58 \times 10^{-4}\ min^{-1} \cdot \mu U^{-1} \cdot ml^{-1}$, respectively; $P < .01$).

To assess the influence of insulin sensitivity on insulin secretion, we examined the relationship between S_I and the various estimates of insulin secretion described above in the 21 nondiabetic controls of varying degrees of adiposity (12 matched and 9 unmatched controls). There was a significant relationship between S_I and AIR_{max}, and the best linear correlation was obtained from a plot of ln AIR_{max} vs. ln S_I (ln $AIR_{max} = -0.59$ ln $S_I + 6.38$; $r = -.68$; $P < .001$; $n = 21$). In view of this relationship and the fact that the indices of insulin sensitivity were significantly different between siblings and their matched controls, the assessment of β-cell function by means of a direct comparison of absolute AIR_{max} is not appropriate. Relative insulin resistance, reflected by lower S_I values, is associated with increased insulin responses, whereas insulin sensitivity, with high S_I values, is associated with low responses. The siblings, however, do not conform to this relationship, with AIR_{max} in 11 of the 12 individuals falling below the regression line of the controls; i.e., for the lower S_I, maximal acute insulin secretory capacity was inappropriately low (Fig. 1). When adjusted for the difference in S_I, the mean ln of AIR_{max} in the siblings (5.82) was lower than in the controls (6.25; $P < .01$).

A linear relationship was also observed between S_I and AIR_{gluc} in nondiabetic controls (ln $AIR_{gluc} = -0.78$ ln S_I + 7.35; $r = -.62$; $P < .005$; $n = 21$). Values of 10 of the siblings fell below the regression line of the controls, indicating that their absolute AIR_{gluc} value is also inappropriately low for their degree of insulin sensitivity (Fig. 2). When adjusted for the difference in S_I, the mean ln of AIR_{gluc} in the

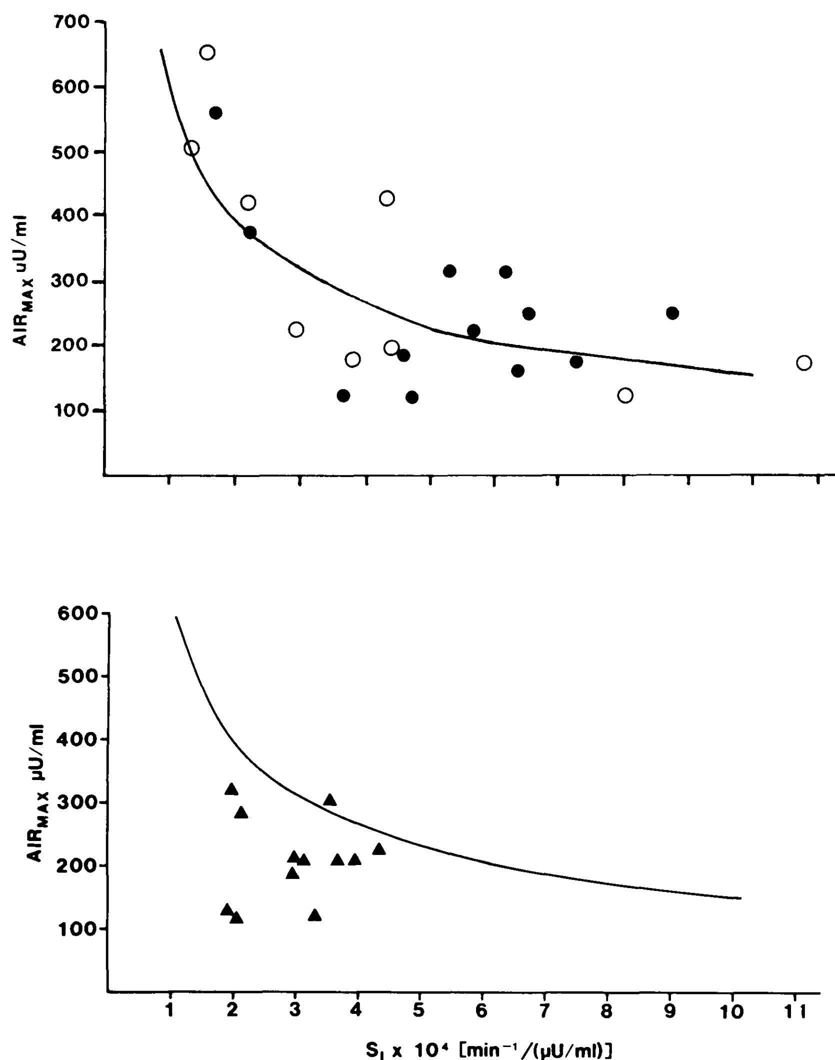

FIG. 1. Relationship between maximum acute insulin response to arginine (AIR_{max}) and insulin sensitivity (S_I) in matched control subjects (●) and other controls (○) and HLA-identical siblings (▲). Regression line in *bottom panel* is relationship in nondiabetic controls.

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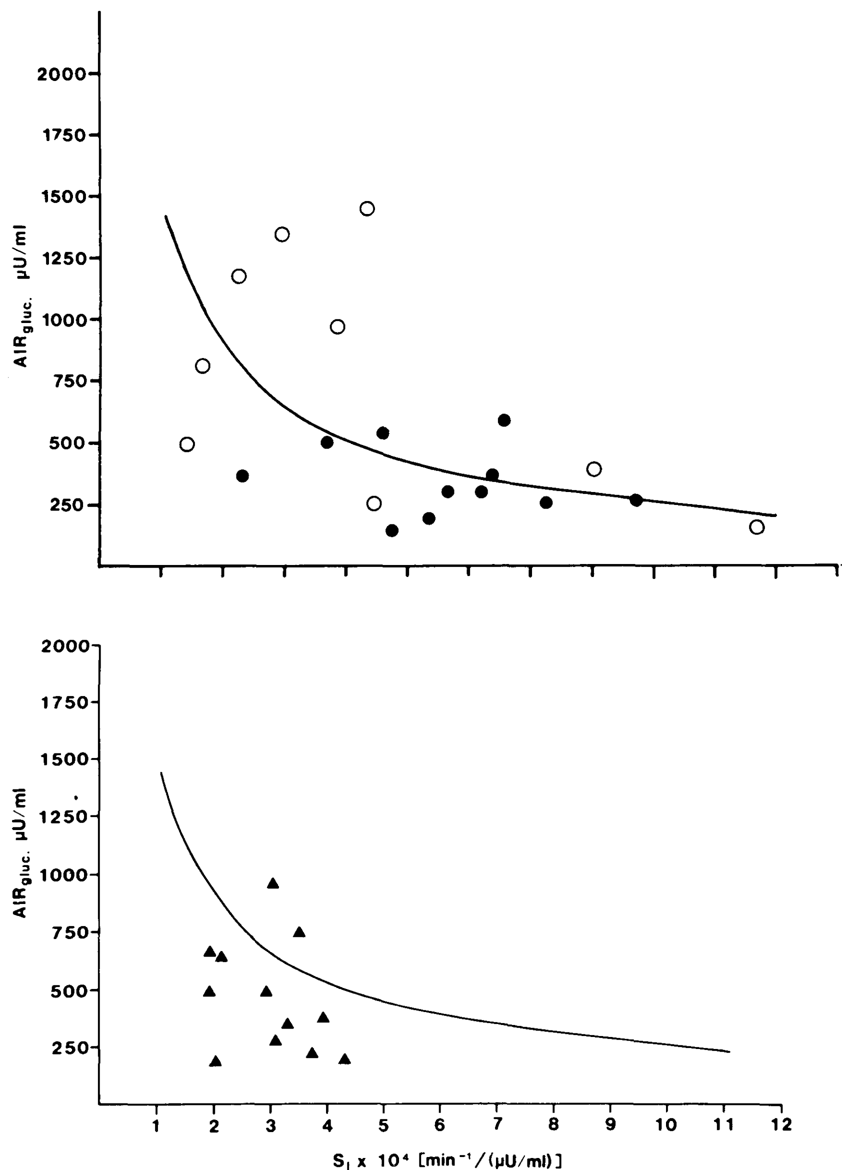

FIG. 2. Relationship between acute insulin response to glucose (AIR_{gluc}) and insulin sensitivity (S_I) in matched control subjects (●) and other controls (○) and HLA-identical siblings (▲). Regression line in *bottom panel* is relationship in nondiabetic controls.

siblings (6.79) is in fact significantly lower than that of the controls (7.31; $P < .05$).

The slope of glucose potentiation is also related to S_I, and the best fit is obtained with a logarithmic plot (ln slope = $-0.61 \ln S_I + 0.94$; $r = -.60$; $P < .01$; $n = 21$). Values of all 12 of the siblings fell below the control regression line (Fig. 3), and when adjusted for the lower S_I, the slope of glucose potentiation was also lower in the siblings. The mean ln slope was 0.47 in the siblings and 0.88 in controls ($P < .025$).

The relationship between the second phase of insulin secretion to glucose and insulin sensitivity also shows an inverse correlation (ln second-phase insulin = $-0.67 \ln S_I + 7.83$; $r = -.71$; $P < .001$; $n = 21$). Values of 11 of the siblings fell below the regression line, displaying inappropriately low second-phase insulin release for their degree of insulin sensitivity. When adjusted for the difference in S_I, this measurement of insulin secretion is also significantly lower than that of the controls. The mean ln of second-phase insulin secretion was 7.36 in the siblings and 7.83 in controls ($P < .025$). No correlation was detected between the AIR_{arg} at fasting glucose level and S_I ($r = .33$).

Levels of the catecholamines norepinephrine and epinephrine in siblings at fasting glucose levels were similar to those obtained in controls (220 ± 40 vs. 248 ± 33 and 50 ± 9 vs. 54.5 ± 10 pg/ml). Levels of norepinephrine and epinephrine in the two groups at glucose levels of ~600 mg/dl before measuring AIR_{max} were also similar (208 ± 32 vs. 271 ± 30 and 51 ± 9 vs. 55 ± 13 pg/ml in siblings and controls, respectively).

In a previous study, we reported an exaggerated AIR_{gluc} in nine HLA-identical siblings compared with that of matched nondiabetic controls (12). Seven of these siblings were restudied as participants in this study, and the insulin responses for each individual are shown in Fig. 4. None of the controls were the same as studied previously, but the mean values were similar. All seven siblings had a lower AIR in this study than in the original test. Four still had the highest AIR_{gluc} in this study (nos. 3, 4, 8, and 12), four still had a higher response than their controls (nos. 3, 4, 8, and 11),

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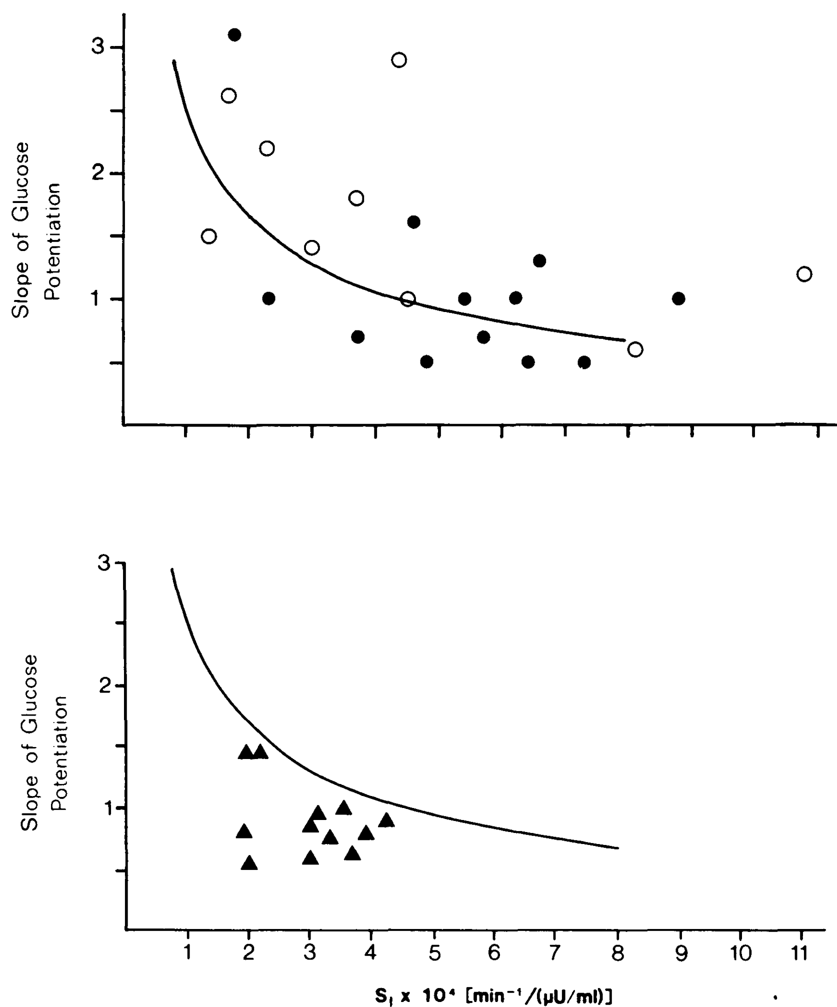

FIG. 3. Relationship between slope of glucose potentiation and insulin sensitivity (S_I) in matched control subjects (●) and other controls (○) and HLA-identical siblings (▲). Regression line in *bottom panel* is relationship in nondiabetic controls.

and one (no. 12) was only lower by virtue of a very high response in the control. In two of the siblings (nos. 5 and 7), there was a large fall in AIR_{gluc} (1150 to 344 and 850 to 171 μU/ml, respectively). Both of these siblings now had low indices of insulin sensitivity (3.3 and 2.5, respectively), and thus their AIR_{gluc} values were greatly reduced when adjusted for their degree of insulin sensitivity.

DISCUSSION

In a previous study, we showed that this group of nondiabetic HLA-identical siblings of insulin-dependent diabetics showed evidence of insulin resistance with a reduced S_I (16). This study examines several different measures of insulin secretion in the same group of subjects, by both direct comparison with matched controls and comparison with a group of nondiabetics, adjusting for differences in S_I.

The AIR_{max} values were lower in these siblings than in their matched controls. We believe that AIR_{max} is an index of the maximal glucose-regulated insulin secretory capacity of the islet and may be related to residual β-cell mass. No differences were detectable in the absolute values of the other measures of insulin secretion when siblings were compared with matched controls. However, among healthy controls a relationship clearly exists between S_I and insulin secretion such that a lower degree of S_I is associated with greater insulin secretion. This relationship must be considered when any comparison of insulin secretion is being made between groups differing in S_I, as in this study.

In nondiabetics, insulin secretion is inversely related to the S_I independent of the percent of ideal body weight. Thus, although commonly used, a direct comparison between groups susceptible to diabetes and controls matched only for age, sex, height, and body weight may not be appropriate and can result in conclusions different from those obtained when β-cell function is evaluated with adjustments for differences in S_I. When adjusted for the difference in S_I between the siblings and nondiabetics, not only was the maximum insulin secretory capacity lower but the acute and second-phase insulin responses to glucose and the slope of glucose potentiation were all significantly lower in the siblings. Thus, these HLA-identical nondiabetic siblings show evidence not only of insulin resistance but of impaired β-cell function. Because this method of quantifying β-cell function depends on simultaneous assessment of S_I, the validity of this interpretation depends on the validity of the measurement of S_I.

Investigators at the Joslin Clinic recently published prospective studies in individuals genetically susceptible to developing IDDM. Their aim was to identify and quantify β-cell destruction by measuring insulin secretion in response to

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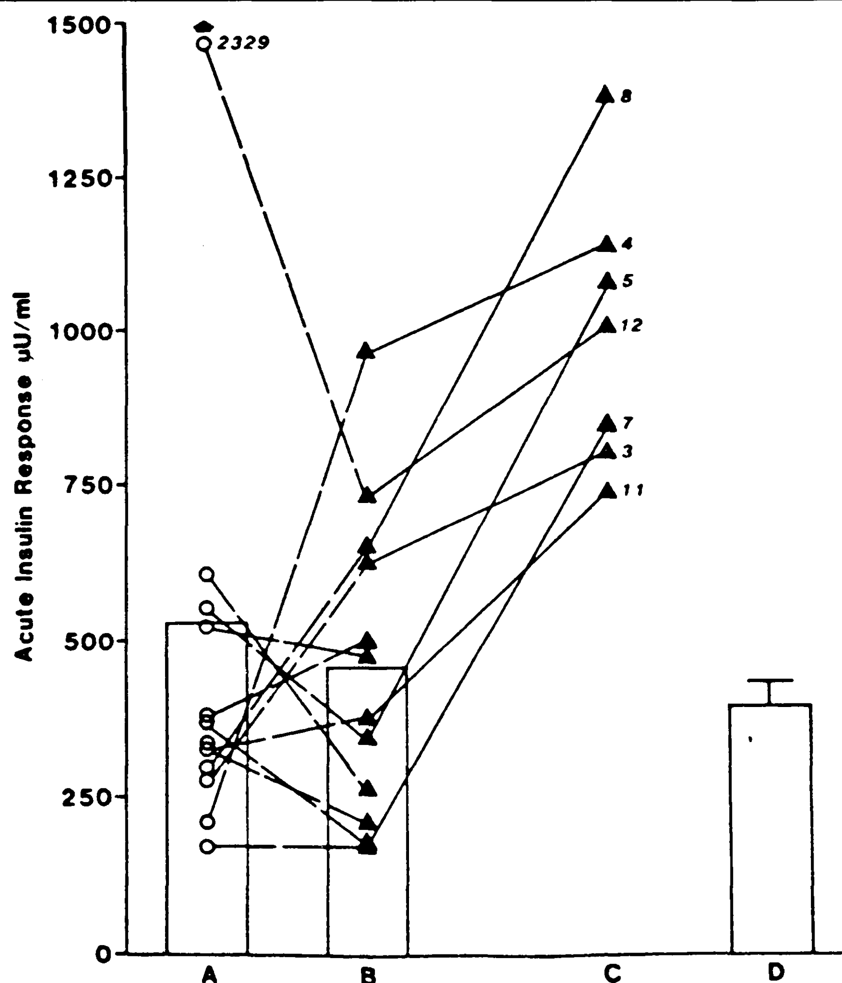

FIG. 4. Acute insulin response (AIR_{gluc}) in this study in siblings (*B*) and matched controls (*A*) compared with response from 7 of the same siblings tested in 1981 (*C*) and mean control population in that study (*D*).

various secretagogues. In those individuals who later developed diabetes, loss of the AIR to intravenous glucose appeared to be the earliest abnormality, whereas the responses to oral glucose and intravenous arginine at fasting glucose concentrations, although abnormal, were still relatively preserved (9–11,29). They interpreted these results as indicating that a loss of the AIR_{gluc} is an early marker of β-cell dysfunction and that the insulin response to other secretagogues may provide a means of quantifying the degree of β-cell loss (29).

In the subjects who have not yet developed diabetes, however, repeated measurements of the AIR to intravenous glucose have shown it to be very variable (11). In some individuals it remains very low, whereas in others the response can decrease and then increase. Some of these variations in the AIR could be physiological adaptations to changes in S_I. Quantifying both S_I and insulin secretion, as in this study, allows adjustment for physiological variations and may provide a more accurate means of estimating β-cell dysfunction. In individuals with normal β-cell function, insulin secretion may change with time, but it would be appropriate for changes in S_I, and the responses would still fall along a regression line such as those shown in Figs. 1–3. In individuals with impaired β-cell function, the insulin response will diminish, but in a manner inappropriate for their S_I. When plotted, in comparison to normal controls, the responses would fall below the regression line.

In this study we did not find a significant difference in the absolute AIR to intravenous glucose between HLA-identical siblings and their matched controls. This is at variance with our previous study, in which we found a higher insulin response in the HLA-identical siblings (12). A possible explanation is that had they been measured, the siblings with hyperinsulinemia in the original study would have been found to have a low S_I. Four of the 7 siblings restudied still have the highest AIR of the 12 in this study (nos. 3, 4, 8, 12). Three of these 4 have a higher response than their controls, and the 4th has a higher response than the mean of the controls. Figure 2 shows that these siblings in fact have the four points nearest the regression line of the controls, suggesting that their islet function is still closest to normal. The 2 siblings who show the largest reduction in AIR_{gluc} also have low S_I values, and therefore the AIR_{gluc} values are inappropriately low. Both also show inappropriately low AIR_{max} values for their degree of insulin sensitivity, and thus the fall seen in the 2 siblings may clearly reflect β-cell dysfunction that has occurred during the 3 yr since the original study. We therefore hypothesize that the hyperinsulinemia observed in the initial study was probably associated with the reduced S_I we observed in HLA-identical siblings. Some of the siblings still

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have an appropriate or hyperinsulinemic response, whereas in others a "normal" but probably inappropriately low response is detected, indicating β-cell dysfunction.

The etiology of the reduced S_I is undetermined. Insulin resistance can occur in newly diagnosed insulin-dependent diabetics (30). This may partly be a consequence of poor metabolic control (31,32), although there is evidence that, despite short-term improvements in control, the abnormality in glucose utilization persists (33). Insulin deficiency induced in rats and dogs by the administration of streptozocin or alloxan has resulted in an absence of insulin resistance in control animals (34,35). In rats treated with streptozocin neonatally and studied 4 wk later, evidence of insulin resistance can be demonstrated in isolated adipocytes, although the postprandial plasma glucose levels in these animals are not significantly higher than those in controls (36). Thus, insulin resistance may be a secondary phenomenon induced by insulin deficiency, which may in some cases be insufficient to increase postprandial hyperglycemia. The rats treated neonatally with streptozocin do, however, have markedly impaired intraperitoneal glucose tolerance. The siblings in our study all have a normal fasting plasma glucose, and none showed impaired intravenous glucose tolerance. Therefore, it is unknown whether the impaired islet cell function demonstrated in these siblings could be sufficient to induce insulin resistance.

Approximately 30% of HLA-identical siblings will develop diabetes before the age of 30 yr (37), but most of these could be expected to have developed the disorder before this age. None of the siblings at the time of this study had detectable islet cell antibodies, and in view of their age and period of discordance from the diagnosis of diabetes in their diabetic siblings, their risk of developing diabetes appears to be low. Thus, the results of this study are unexpected in that they show the group as a whole to have evidence of β-cell dysfunction, which suggests that β-cell dysfunction may occur with a much greater frequency in such individuals than previously thought. Immune markers, such as an increase in the percentage of activated T-lymphocytes, are seen in a large proportion of unaffected identical twins (38) and HLA-identical siblings (39) (more than would be expected to actually develop the disorder), and recently a large screening program of school-age children showed a prevalence of islet cell antibodies, approximately double the number expected to develop clinical IDDM (40). If the siblings we studied had been tested when diabetes was diagnosed in their HLA-identical siblings, immune markers may have been detected in at least some. The evidence of β-cell dysfunction presented here, in conjunction with the above reports of immune markers in individuals thought unlikely to develop IDDM, suggest that β-cell destruction may occur in a much greater proportion of genetically susceptible individuals than previously thought. It is possible that this destructive process persists or recurs and progresses toward frank IDDM in only a minority. Stated another way, our data are compatible with the hypothesis that IDDM as a disease process resulting in β-cell damage may not always progress to clinical IDDM and therefore encompasses a broad spectrum with clinical IDDM being the severest form but subclinical IDDM being much more common.

Whether the reduced S_I in these HLA-identical siblings plays a role in the susceptiblity toward developing IDDM remains unknown. Such a difference in sensitivity, however, highlights the importance of accounting for this variable when measures of insulin secretion are being used as estimates of residual β-cell mass. Prospective studies of insulin secretion should employ a measure of S_I such that β-cell function can be analyzed as above. This may allow earlier detection of β-cell dysfunction and more accurate quantification of serial β-cell function in individuals predisposed toward developing IDDM. This methodology should also be utilized in studies in which the efficacy of preventative therapeutic intervention is being evaluated.

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