Elevated Serum Human Growth Hormone and Decreased Serum Insulin in Prediabetic Males after Intravenous Tolbutamide and Glucose

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ABSTRACT Serum human growth hormone (HGH), serum immunoreactive insulin (IRI), plasma free fatty acids, and blood glucose were measured during intravenous glucose and intravenous tolbutamide tolerance tests in 13 normal and 13 prediabetic (offspring of two diabetic parents) males, closely matched for weight and age. Only prediabetics with normal glucose tolerance during oral, intravenous, and cortisone-primed glucose tolerance tests were evaluated.

Mean serum HGH levels were significantly higher in prediabetics in response to intravenous tolbutamide and at the end of the 3-hr intravenous glucose tolerance tests (IVGTT). This is interpreted as a hyperresponsiveness of the growth hormone-releasing mechanisms in prediabetic subjects.

The insulin response during the first 10 min of an IVGTT was significantly reduced in prediabetic males as compared to normal controls, whereas the insulin response to intravenous tolbutamide was not significantly different at the same time intervals in the same subjects.

It appears, therefore, that measuring IRI during an IVGTT can be valuable in detecting the earliest signs of diabetes even before any disturbance of blood glucose homeostasis is seen.

The possibility that growth hormone hypersecretion in prediabetics might play a role in the pathogenesis of human diabetes mellitus is discussed.

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INTRODUCTION

The prediabetic state has been defined as the period between conception and the time a definitive diagnosis of diabetes can be made by present methods of testing in a genetically predisposed subject (1, 2). There is some evidence that biochemical and histological changes are already present during this period. An increase in the thickness of basement membranes in glomerular (3) and muscle capillaries (4), elevated fasting levels of serum insulin-like activity (ILA) (5), and a blunted early serum insulin response with excessive later response to massive oral glucose loads have all been reported (6).

This present study was designed to evaluate levels of serum human growth hormone, a known diabetogenic substance, and serum insulin, a key regulator of carbohydrate metabolism in normals and prediabetics. These hormones, free fatty acid concentrations, and blood sugar levels were measured during intravenous tolbutamide tolerance tests (IVTTT) and intravenous glucose tolerance tests (IVGTT) in prediabetic males (offspring of two diabetic parents) and in a control group of normal males closely matched for age and weight. Female subjects were not studied since the known sex difference in HGH concentration would have

rendered evaluation of HGH levels difficult. All prediabetics showed normal blood glucose levels during oral glucose tolerance tests (100 g of glucose), during cortisone-primed oral glucose tolerance tests, and during intravenous glucose tolerance tests. Furthermore, there were no statistically significant differences between the mean blood glucose levels achieved by the normals and the prediabetics on these tests. Previous studies in normal subjects have shown that tolbutamide stimulates both HGH and IRI secretion (7, 8), and intravenous glucose enhances insulin secretion and frequently produces rises of serum HGH 90 min or more after glucose infusion.

The data reported here indicate that: (*a*) prediabetic males had higher levels of serum HGH than did normal males in response to intravenous tolbutamide and glucose; (*b*) prediabetic males exhibited a significantly reduced serum insulin response immediately after injection of glucose; and (*c*) the insulin response after injection of tolbutamide in prediabetic males was *not* different from normal controls.

METHODS

The IVTTT and IVGTT were performed in 13 normal males, ranging in age from 19 to 43 yr (mean, 27.8 yr) and ranging from 95 to 116% of their ideal weight[1] (mean, 103.8%). None had a family history of diabetes. The 13 prediabetic males observed in this study ranged in age from 16 to 42 yr (mean, 27.8 yr), were nonobese (weight range, 96–116% of ideal weight; mean, 105.6%), and each was an offspring of two well-documented diabetic parents. (IVTTT was performed in only 11 of the prediabetics.) All prediabetics had normal blood sugar values during previously performed oral (100 g), intravenous (0.5 g/kg), and cortisone-primed glucose tolerance tests (9), and except for subjects S. A. and S. R., were not related to each other. For 3 days before the IVTTT and IVGTT, the diet of all subjects contained 300 g of carbohydrate per day.

The tests were performed after an overnight fast and a 20 min period of recumbency. For the IVTTT, 1 g of tolbutamide[2] dissolved in 20 ml of saline was infused into an antecubital vein during a 3-min period. For the IVGTT, glucose (0.5 g/kg of body weight) was injected intravenously in 3 min as a 25% solution. Blood samples were drawn from an indwelling needle in an antecubital vein kept patent with a slow infusion of isotonic saline. Samples were obtained at 0, 1, 3, 5, 10, 20, 30, 40, 50, 60, 90, 120, and 180 min after termination of the glucose or tolbutamide injection.

[1] From Metropolitan Life Insurance Tables, 1959.

[2] Orinase Diagnostic, 1.0 g, courtesy of the Upjohn Co., Kalamazoo, Mich.

Blood sugar was determined by the ferricyanide method of Hoffman, modified for use with the AutoAnalyzer (Technicon Instruments Corporation, Chauncey, N. Y.) (10). Serum HGH and insulin (IRI) were measured by double antibody radioimmunoassay techniques (7, 11). All HGH levels in this study were determined in a single assay in order to exclude possible fluctuations from assay to assay. The serum samples were assayed for IRI in a totally random fashion. Reproducibility in these assays was assured by using a quality control system, i.e., the same pooled serum was tested in each assay, and aliquots of the same human insulin standards were utilized in each assay.[3] Free fatty acids were measured according to Dole and Meinertz (12).

RESULTS

Blood sugar responses

The mean fasting blood sugar before the tolbutamide infusion was 76 mg/100 ml in both normals and prediabetics (Table I). After the infusion, the mean blood sugar level decreased at 30 min to 44 mg/100 ml in normals and to 43 mg/100 ml in prediabetics. Thereafter, the blood sugar began to rise, but at 3 hr it was still somewhat lower than the mean fasting level.

During the IVGTT (Table I and Fig. 1), normals and prediabetics reached the highest mean blood sugar concentration 1 min after injection of glucose (321 and 314 mg/100 ml, respectively). Thereafter, glucose concentrations declined rapidly in both groups and were lower than the fasting levels at 90 min. The mean K rate of glucose disappearance was 2.34 (range, 1.52–3.28) in normals and 2.12 (range, 1.25–5.41) in prediabetics. The difference was not significant.

Serum HGH responses

IVTTT (Table II and Fig. 2). The mean fasting HGH was 1.3 mμg/ml in normals and 1.6 mμg/ml in prediabetics. Mean HGH levels reached peak values at 90 min in normals (11.4 mμg/ml) and at 60 min in prediabetics (21.7 mμg/ml). Mean HGH levels in prediabetics were significantly higher than in normal controls at 40, 50, and 60 min. Maximum HGH levels in the prediabetics ranged from 0.8 to 80 mμg/ml, whereas in the normals it ranged from 5 to 25 mμg/ml.

Considerable variability of serum HGH response occurred in both groups. In the normal subjects, increments over fasting HGH levels

[3] Courtesy of Dr. Mary A. Root, Lilly Research Laboratories, Eli Lilly and Company, Indianapolis, Ind.

TABLE I

Blood Sugar (BS), Human Growth Hormone (HGH), Immunoreactive Insulin (IRI), and Free Fatty Acids (FFA) during i.v. Tolbutamide and i.v. Glucose Tolerance Tests (IVTTT and IVGTT) in Normal and Prediabetic Males (Mean ±SEM)

Min..... 0	1	3	5	10	20	30	40	50	60	90	120	180
					BS mg/100 ml							
IVTTT												
Normals	76.4	75.1	74.1	72.4	66.5	54.5	44.1	42.5	48.2	52.8	61.5	64.8	69.2
n = 13	± 1.4	± 1.7	± 1.6	± 1.5	± 1.8	± 2.0	± 2.7	± 2.0	± 1.6	± 1.6	± 1.3	± 1.4	± 1.4
Prediab	76.0	74.4	74.2	72.7	65.4	54.1	43.1	46.3	51.7	54.6	60.4	64.4	68.0
n = 11	± 1.4	± 1.5	± 1.6	± 1.4	± 1.9	± 2.4	± 2.9	± 2.1	± 1.5	± 1.9	± 1.2	± 0.9	± 1.2
IVGTT													
Normals	75.9	321.2	303.2	282.4	254.2	196.9	155.1	125.0	100.5	84.8	63.2	63.1	69.5
n = 13	± 1.8	± 12.8	± 11.0	± 7.9	± 5.2	± 5.5	± 5.5	± 5.6	± 6.2	± 4.7	± 1.8	± 1.8	± 1.8
Prediab	78.5	314.2	295.9	275.2	245.5	198.2	163.3	136.7	112.5	97.0	66.7	62.8	67.2
n = 13	± 2.0	± 8.0	± 7.4	± 6.3	± 4.4	± 6.9	± 9.0	± 9.3	± 8.2	± 7.0	± 2.5	± 2.4	+ 2.5
IVTTT						See Table II							
					HGH mμg/ml							
IVGTT													
Normals	0.5	0.4	0.4	0.4	0.4	0.6	0.6	0.7	0.7	0.7	0.6	2.1	3.4
N = 13	± 0.06	± 0.04	± 0.05	± 0.05	± 0.04	± 0.07	± 0.08	± 0.17	± 0.18	± 0.21	± 0.04	± 1.25	± 1.33
Prediab	1.4‡	2.0	2.1	2.1	2.3	3.0	2.8	2.8	2.0	1.5	1.0	1.3	15.8*
N = 13	± 0.3	± 0.7	± 0.9	± 1.1	± 1.2	± 1.9	± 1.7	± 1.7	± 1.0	± 0.5	± 0.2	± 1.5	± 5.7
					IRIμU/ml							
IVTTT													
Normals	20.1	114.3	107.8	103.5	86.8	60.8	41.3	29.6	25.9	23.2	21.0	20.1	18.5
N = 13	± 4.4	± 17.9	± 17.2	± 17.6	± 18.8	± 15.9	± 9.5	± 6.4	± 5.0	± 4.9	± 4.4	± 4.8	± 4.4
Prediab	21.4	128.4	109.2	94.1	74.5	47.3	32.2	24.0	24.6	20.7	18.5	18.8	17.2
n = 11	± 3.4	± 18.0	± 16.8	± 14.6	± 12.2	± 6.4	± 4.1	± 3.8	± 3.7	± 2.6	± 2.8	± 3.1	± 2.8
IVGTT						See Table III							
					FFA μEq/liter							
IVTTT													
Normals	487				521	458		387		425	497	548	672
n = 13	± 38				± 28	± 22		± 21		± 37	± 27	± 33	± 29
Prediab	425				433	373		368		427	435	484	605
n = 11	± 38				± 36	± 24		± 15		± 38	± 43	± 62	± 73
IVGTT													
Normals	547				460	363		275		247	280	330	559
n = 13	± 29				± 26	± 25		± 17		± 15	± 22	± 29	± 39
Prediab	496				423	331		269		235	238	312	485
n = 13	± 54				± 41	± 28		± 18		± 13	± 15	± 26	± 40

* $p < 0.05$. ‡ $p < 0.01$.

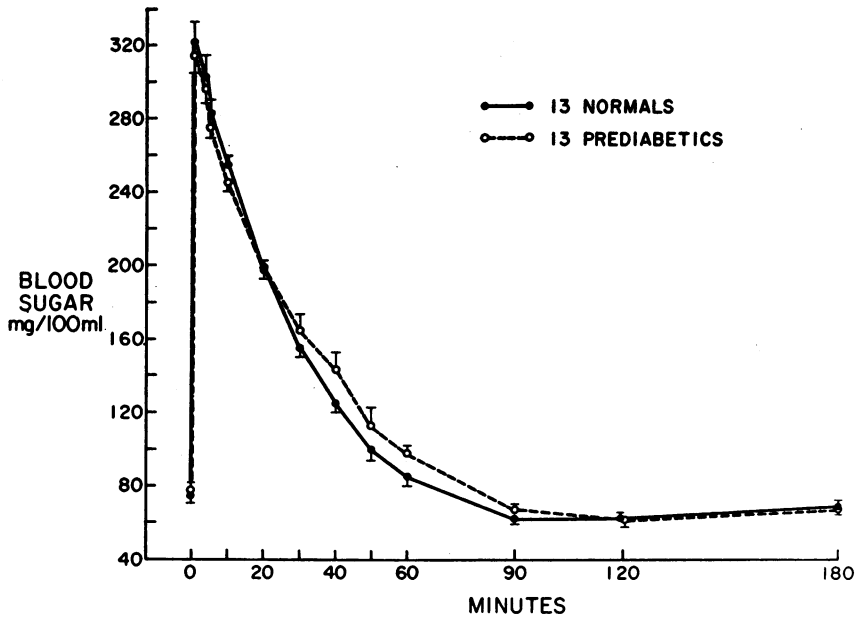

FIGURE 1 Mean (and SEM) levels of blood sugar in prediabetic and normal males during intravenous glucose tolerance tests.

ranged from 0.7 (R. R.) to 25.4 mμg/ml (D. J.). In the prediabetics, the smallest increment seen was 0.4 (F. W.), the greatest was 79.5 mμg/ml (W. J.). Furthermore, considerable overlap between the two groups was present. However, 8 of the 11 prediabetics had one or more levels of serum HGH that exceeded the highest individual level seen in the normal group (indicated in Table II by double dagger). Three of the prediabetics (L. A., W. J., and B. D.) exceeded the highest of

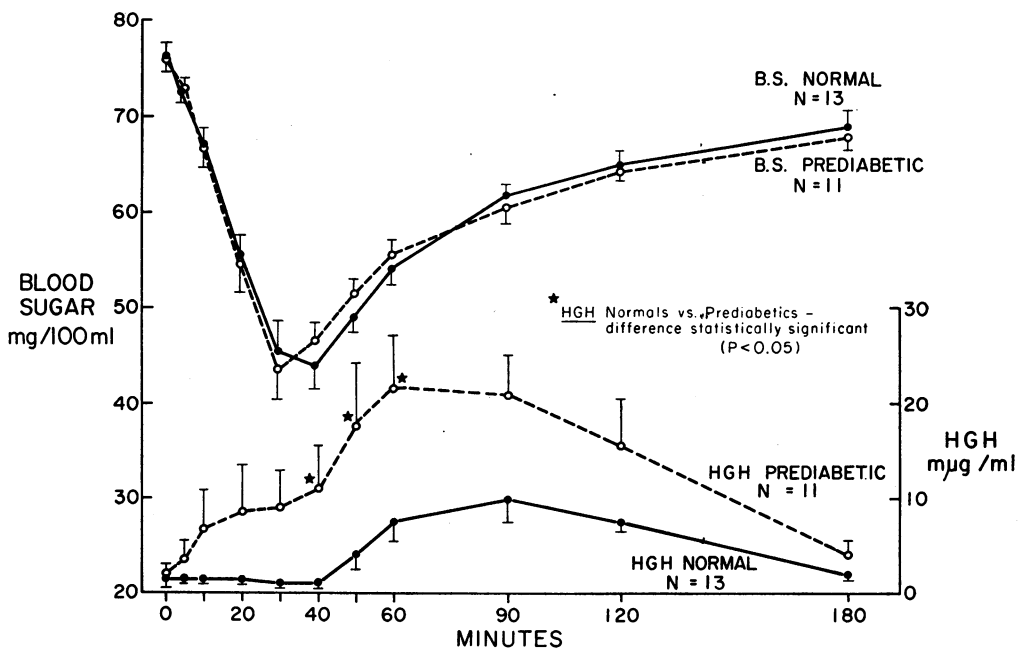

FIGURE 2 Mean (and SEM) levels of serum human growth hormone and blood sugar in prediabetic and normal males during intravenous tolbutamide tolerance tests.

TABLE II

Serum Growth Hormone (mμg/ml) during i.v. Tolbutamide Tests Performed on 13 Normal and 11 Prediabetic Male Subjects

Subject	Age	% ideal weight	Minutes 0	5	10	20	30	40	50	60	90	120	180
	yrs												
Normals													
G. H.	43	104	6.5	7.9	6.2	6.0	4.0	2.4	2.1	1.9	18.7	13.6	3.1
B. G.	23	103	0.4	0.5	0.6	0.9	0.8	0.6	0.6	0.8	22.0	7.9	1.2
B. R.	26	96	1.1	1.6	1.4	0.5	0.7	0.9	8.0	14.4	4.8	2.4	1.2
B. F.	29	102	1.5	1.8	1.4	1.0	1.5	2.4	16.4	22.0	13.2	6.2	1.9
C. C.	28	104	0.3	0.6	0.5	0.6	0.7	0.5	0.7	2.0	12.8	3.8	0.5
D. J.	32	103	0.4	0.6	0.4	0.4	0.4	0.4	0.4	0.4	16.0	25.0	2.7
G. M.	31	106	1.5	1.4	1[85]	1.2	1.2	1.1	8.0	17.2	11.2	6.6	2.3
J. C.	20	107	0.5	0.5	0.5	0.5	0.5	0.6	0.6	1.1	0.4	10.6	5.5
K. M.	19	116	0.9	0.9	0.5	0.6	0.6	0.9	7.2	23.6	8.0	2.7	—
R. R.	25	109	1.8	1.3	1.5	1.5	1.4	1.6	2.5	4.5	2.4	1.2	1.5
S. J.	34	107	0.4	0.4	0.3	0.4	0.4	0.5	0.5	4.0	24.0	8.5	2.2
W. G.	29	95	0.5	0.3	0.3	0.4	0.4	0.9	2.4	2.0	13.6	6.2	1.5
H. C.	23	97	0.4	0.4	0.4	0.4	0.4	0.4	3.2	8.0	1.0	0.5	0.4
Mean	27.8	103.8	1.3	1.4	1.2	1.1	1.0	1.0	4.1	7.9	11.4	7.3	2.0
±SEM			0.5	0.6	0.4	0.4	0.3	0.2	1.3	2.4	2.1	1.8	0.4
Prediabetics													
F. W. (a)*	33	100	0.4	0.4	0.4	0.4	0.4	0.4	0.4	0.4	0.8	0.8	0.4
F. C. (b)	39	100	0.9	0.4	0.7	0.3	0.4	33.0‡	23.0‡	19.2	26.8‡	16.0	1.8
H. D. (c)	42	106	0.7	0.7	0.4	0.3	0.7	4.0‡	26.0‡	36.0‡	22.8	22.5	4.4
K. S. (d)	16	96	0.7	0.7	1.1	0.5	0.6	0.6	8.0	26.8‡	34.0‡	16.5	2.1
S. R. (a)	34	107	0.7	0.4	0.7	0.7	0.7	0.7	0.7	0.5	2.7	1.1	0.4
V. A. (c)	31	106	0.8	0.6	0.7	0.8	0.7	1.3	12.5	24.0‡	14.7‡	13.4	4.2
W. J. (c)	27	107	0.5	1.4	2.9	10.3‡	32.0‡	47.6‡	80.0‡	64.0‡	52.0‡	64.0‡	4.9
Z. N. (d)	18	116	0.5	0.4	0.4	0.4	0.4	0.4	0.4	3.6	9.2	6.0	0.5
B. D. (d)	18	101	0.2	2.0	5.0	7.5‡	10.5‡	18.4‡	26.8‡	26.0‡	18.4	4.9	0.6
L. A. (b)	16	117	12.5‡	20.0‡	22.5‡	28.5‡	26.5‡	20.8‡	31.2‡	38.0‡	48.0‡	27.5‡	14.0‡
G. R. (d)	39	100	0.4	0.2	0.2	0.3	1.0	3.2‡	0.5	0.3	0.2	0.2	14.5‡
Mean	28.5	105.1	1.6	3.4	6.8	8.5	9.0	11.9	19.0	21.7	20.8	15.3	4.1
±SEM			1.0	1.9	4.1	4.6	3.9	4.9	7.1	6.0	4.9	5.1	1.4
P (*t* test)§			NS	NS	NS	NS	NS	<0.05	<0.05	<0.05	NS	NS	NS

NS, not significant.

* (a) Both parents treated with insulin; (b) both parents treated with diet only; (c) one parent treated with oral hypoglycemic agent, the other with insulin; (d) one parent treated with diet, the other with oral hypoglycemic agent; (e) both parents treated with oral hypoglycemic agent.

‡ Level exceeds highest individual level in normals.

§ Difference normals vs. prediabetics.

the normal values at 11, 7, and 5 time intervals respectively. At both the 40 and the 60 min time intervals, HGH levels in 6 of the 11 prediabetics exceeded those of the highest normals. There appeared to be no relationship between the prediabetics who exhibited the greatest abnormality in serum HGH levels (L. A., W. J., and B. D.) and the severity of the diabetes in their parents, at least as evaluated by the treatment requirements of the parents. The parents of L. A. required only dietary therapy, one parent of W. J. required oral hypoglycemic agents and the other insulin, and one parent of B. D. required an oral agent and the other diet only. Prediabetics F. W. and S. R. were offspring of two insulin-treated parents, but neither of these prediabetics exhibited any abnormalities of serum HGH. In almost all instances, the parents were unavailable for examination, and only hospital and attending physician records were available for inspection.

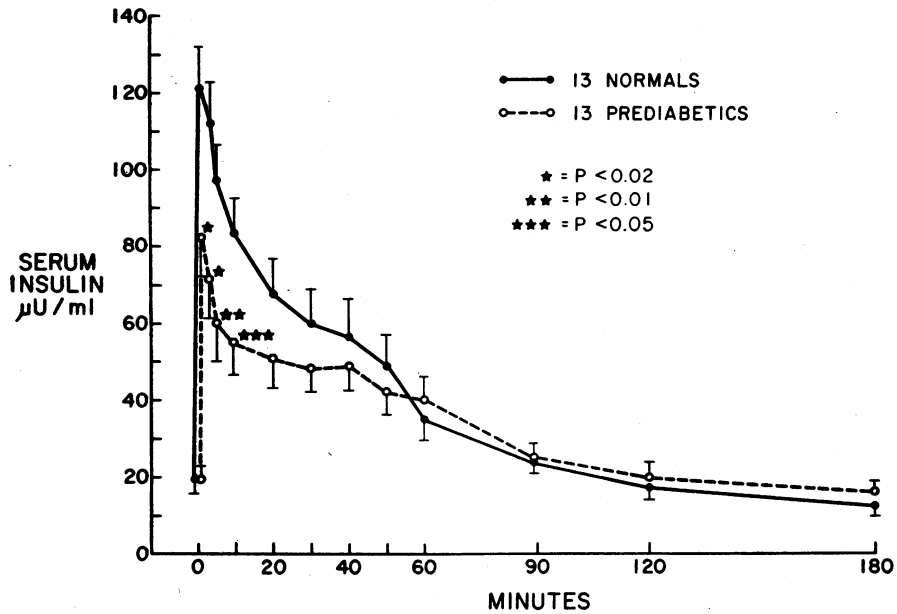

FIGURE 3 Mean (and SEM) levels of serum insulin in prediabetic and normal males during intravenous glucose tolerance tests. P values calculated with t test.

IVGTT (Table I). The mean fasting serum HGH was 0.5 mμg/ml in normals and 1.4 mμg/ml in prediabetics ($P < 0.05$). Thereafter, the only significant difference in mean levels of serum HGH was at the 180 min interval when the mean HGH level was 15.8 mμg/ml for prediabetics and 3.4 mμg/ml for normals ($P < 0.05$). Four prediabetics exceeded the maximal level of HGH (16.5 mμg/ml) seen in the normal group with values of 18, 40, 40, and 59 mμg/ml.

Serum insulin responses

IVTTT (Table I). The mean fasting IRI levels were 20 μU/ml in normals and 21 μU/ml in prediabetics. 1 min after injection of tolbutamide there was a sharp rise to a mean level of 114 μU/ml in normals and 128 μU/ml in prediabetics, followed by an equally rapid decrease of serum insulin levels in both groups. At no time during the test were the IRI levels significantly different between prediabetics and normals.

IVGTT (Fig. 3 and Table III). The mean fasting IRI levels were 20 μU/ml in normals and 20 μU/ml in prediabetics. The serum IRI increased to a level of 122 μU/ml in normals but to only 82 μU/ml in prediabetics 1 min after glucose administration. Significantly higher mean IRI values were seen in normals at the 1, 3, 5, and 10 min intervals. The serum IRI concentration decreased thereafter at a rapid rate in normals, but at a slower rate, between 10 and 60 min, in the prediabetics. All 13 controls reached their maximum IRI concentration at the 1 or 3 min interval and achieved IRI levels higher than 70 μU/ml. Three prediabetic subjects exhibited a delayed insulin peak which occurred at 40 min in two, and at 50 min in a third. In 5 of the 13 prediabetics, the maximum levels were less than 70 μU/ml. Serum insulin levels were abnormal by these criteria in a total of 7 of the 13 prediabetics, as judged by either a delay in achieving peak serum IRI and (or) a peak IRI level below 70 μU/ml.

Relationships were sought between those prediabetics who exhibited a marked degree of delay in achieving peak serum insulin levels (F. C., K. S., and M. S.) and the severity of the diabetes apparent in the parents. However, none of the six parents required insulin treatment. Of the four prediabetics who showed only abnormally low peak insulin levels (Z. N., B. D., L. A., and G. R.), none of the eight parents was treated with insulin.

A highly significant correlation was found between levels of serum IRI and blood sugar during the IVGTT ($P < 0.01$). Therefore, a linear re-

TABLE III

Serum Insulin (μU/ml) during i.v. Glucose Tolerance Tests Performed on 13 Normal and Prediabetic Male Subjects

Subject	Age	% Ideal weight	0	1	3	5	10	20	30	40	50	60	90	120	180
	yr														
Normals															
G. H.	43	104	16	100*	94	77	72	56	57	57	40	33	24	19	16
B. G.	23	103	15	71*	70	61	44	37	36	41	50	56	43	12	17
B. R.	26	96	15	79*	65	59	41	37	29	28	23	19	15	—	9
B. F.	29	102	22	139*	112	99	91	87	84	83	82	73	38	22	19
C. C.	28	104	58	167*	167	136	132	129	125	132	114	95	59	44	39
D. J.	32	103	10	111*	82	68	46	35	34	33	32	28	10	13	8
G. M.	31	106	16	67	78*	71	66	59	63	58	67	34	24	21	15
J. C.	20	107	11	103	106*	94	71	42	36	26	17	15	9	10	11
K. M.	19	116	31	183*	179	146	139	120	97	78	51	35	25	24	23
R. R.	25	109	21	160*	126	122	118	100	95	87	66	32	18	15	5
S. J.	34	117	12	86*	76	79	51	50	44	41	34	26	20	12	13
W. C.	29	95	16	147*	128	106	84	63	40	34	34	29	16	11	13
H. C.	23	97	13	170	174*	161	120	65	43	47	20	10	11	8	10
Mean	27.8	103.8	19.7	121.8	112.1	97.7	83.2	67.7	60.2	57.3	48.5	36.5	24.0	17.2	15.2
±SEM			3.6	11.4	11.2	9.6	8.8	8.8	8.5	8.5	7.7	6.5	4.1	2.6	2.4
Prediabetics															
F. W.(a)‡	33	100	13	79*	50	38	35	31	28	30	34	35	19	15	13
F. C.(b)	39	100	42	73	56	67	59	84	96	116*	104	97	46	51	40
H. D.(c)	42	106	50	168*	157	127	126	121	99	84	69	69	42	33	32
K.S.(d)	16	96	16	44	35	35	38	35	46	48	57*	48	33	18	15
M.S.(e)	24	108	27	68	52	52	42	50	51	70*	61	62	42	32	35
S. A.(a)	25	109	10	115*	84	64	61	38	35	29	31	20	13	13	10
S. R.(a)	34	107	15	73*	54	49	46	53	55	54	39	20	19	14	10
V. A.(c)	31	106	14	128	138*	128	120	62	25	26	16	11	7	7	—
W. J.(c)	27	107	10	93	99*	65	52	43	36	33	26	22	12	10	6
Z. N.(d)	18	116	14	64*	45	38	29	34	39	35	36	39	19	19	12
B.D.(d)	18	101	8	68*	61	41	30	24	24	26	23	23	14	9	8
L.A.(b)	16	117	19	67*	60	39	55	57	60	54	21	42	28	19	96
G. R.(d)	39	100	16	36*	33	32	31	28	29	32	33	31	28	19	11
Mean	27.8	105.6	19.5	82.1	71.1	59.6	55.7	50.8	47.9	49.0	42.3	39.9	24.8	19.9	16.5
±SEM			3.5	10.0	10.7	9.0	8.8	7.4	6.9	7.5	6.8	6.7	3.6	3.4	3.5
P (*t* test)§			NS	<0.02	<0.02	<0.01	<0.05	NS	NS	NS	NS	NS	NS	NS	NS

NS, not significant ($P > 0.05$).

* Maximum IRI level.

‡ Small letter beside subject, see footnote Table II for code.

§ Difference normals vs. prediabetics.

gression equation was constructed to express this relationship, and a comparison of the slopes of the equations derived for the normals and prediabetics was performed. As can be seen in Fig. 4, a significantly lower serum insulin relationship to blood sugar was found in the prediabetics ($P < 0.01$).

In order to evaluate the influence of age on the insulin response to intravenous glucose, normals and prediabetics were separated into three age groups. As can be seen in Table IV, mean IRI values in all age groups were higher in normals immediately after injection of glucose. Only in the younger age group (15–24 yr of age), however, was the difference statistically significant.

There was no significant relationship between abnormalities in growth hormone and insulin secretion in the prediabetics. Only four of the seven prediabetic males with decreased or delayed peak IRI levels in response to glucose showed also excessive levels of HGH during IVTTT.

TABLE IV

IRI Levels during the First 10 Min after i.v. Glucose Injection in Normals and Prediabetics Separated into Three Age Groups
(*MEAN* ± SEM)

Min..... 0	1	3	5	10
		Age 15–24 yr		
Normals n = 4	17.5 ±4.6	131.8 ±26.8	132.3 ±26.6	115.5 ±23.2	93.5 ±21.8
Prediabetics n = 5	16.8 ±3.1	62.2 ±4.6	50.6 ±4.9	41.0 ±2.9	38.8 ±4.7
*P**	NS	<0.05	<0.02	<0.01	<0.05
		25–34 yr			
Normals n = 8	21.3 ±5.4	119.5 ±13.8	104.3 ±12.4	91.4 ±10.4	79.3 ±11.7
Prediabetics n = 5	12.4 ±1.0	95.8 ±11.4	85.0 ±16.1	68.8 ±15.6	62.8 ±14.9
*P**	NS	NS	NS	NS	NS
		35–44 yr			
Normals n = 1	16.0	100.0	94.0	77.0	72.0
Prediabetics n = 3	36.0 ±10.3	92.3 ±39.3	82.0 ±38.1	74.3 ±27.7	72.0 ±28.2

* *t* test.

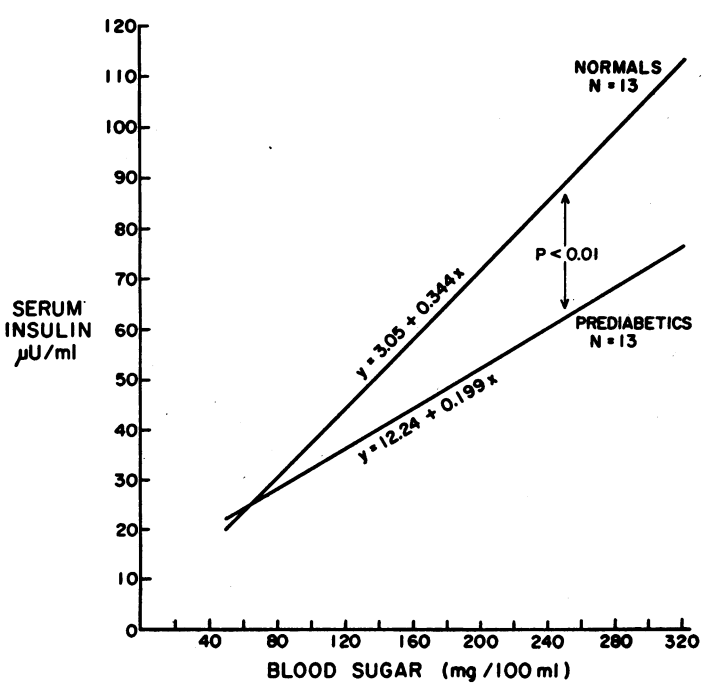

FIGURE 4 Linear regression equations of pooled insulin-blood sugar levels during intravenous glucose tolerance tests in prediabetic and normal males.

Plasma free fatty acids

IVTTT (Table I). The mean fasting FFA levels were 487 μEq/liter in normals and 425 μEq/liter in prediabetics. 40 min after tolbutamide administration mean FFA levels had decreased to 387 μEq/liter in normals and to 368 μEq/liter in prediabetics. After that, the FFA concentration started to rise and reached levels higher than 600 μEq/liter at 180 min in both normals and prediabetics. No significant differences were observed.

IVGTT (Table I). The stimulation of insulin secretion by glucose resulted in a greater decrease of FFA levels compared to tolbutamide which reached nadirs of 247 μEq/liter in normals and 235 μEq/liter in prediabetics at 60 min. Again, the mean FFA levels of normals and prediabetics were not significantly different from each other at any time throughout the tests.

DISCUSSION

The prediabetic subjects observed in this study are offspring of two diabetic parents and were not glucose intolerant during oral, intravenous, and cortisone-primed oral glucose tolerance tests. Their chance, however, of eventually becoming diabetic approaches 100% (13).

In this study of prediabetics and normals, closely matched for weight, age, and sex, it has been found that, although mean fasting insulin levels were not different, the insulin response to intravenous glucose was significantly diminished in prediabetics during the first 10 min of an intravenous glucose tolerance test.

After subdividing the prediabetic group into three age groups, it was apparent that the mean levels of serum IRI were lower than normal subjects at the 1, 3, 5, and 10 min intervals in all groups although only significantly so in the 15–24 yr old subgroup. The small number of subjects in each group, however, makes it difficult to evaluate the meaning of these findings, and only future studies in these selected prediabetic males might provide a clear interpretation.

An analysis of the insulin-glucose relationships during oral and cortisone-primed oral glucose tolerance tests has also been completed in the five prediabetics, age 25–34 yr, and a significantly diminished insulin-glucose relationship has been found (14).

Besides this reduced early response, the apparent rate of decrease in IRI concentration was less in prediabetics during the first 60 min of the test. Assuming an equally large distribution space and turnover rate for insulin in both groups, this would suggest a sluggish insulin response and a slightly prolonged secretion rate of IRI from the prediabetic pancreatic β-cell in response to glucose, as has been shown for mild and moderate diabetics (15, 16). Interestingly, tolbutamide caused an equal IRI response in normals and prediabetics. This finding lends further support to the thesis that glucose and tolbutamide provoke insulin secretion by different mechanisms (17, 18) and suggests that tolbutamide enables the β-cell in the prediabetic to secrete normal amounts of insulin.

7 of the 13 prediabetic subjects were clearly distinguishable from normal controls during the IVGTT either on the basis of a low maximum IRI response or a delay in achieving the IRI peak level. It appears, therefore, that measuring IRI during an IVGTT may prove to be a means of detecting diabetes even before any disturbance of glucose tolerance can be demonstrated.

The question then necessarily arises, what biochemical event, genetically initiated, is responsible for this defect of pancreatic β-cells?

It is well known that injection of anterior pituitary extracts produce permanent diabetes mellitus in dogs and cats (19). In man, injection of 5 mg of HGH (20) or excessive serum levels of growth hormone, such as in acromegaly, cause impairment of glucose utilization (21, 22). Therefore, it has been long suspected that oversecretion of HGH might play a role in the pathogenesis of human diabetes mellitus.

In this study, all fasting HGH values in normals and prediabetics, with the exception of prediabetic L. A. and normal G. H., were within the normal range of 0–3 mμg/ml. However, mean fasting HGH levels were found to be slightly higher in prediabetics than in normal controls on both occasions on which they were tested; and, at the beginning of the intravenous glucose tolerance test, this difference was significant. It is well known that unless fasting HGH is measured in the true basal state (at the moment of awakening), a variety of stimuli can produce significant serum HGH elevations. Therefore, it is difficult to evaluate the heterogeneity of "0 time" serum HGH levels in these normals and prediabetics because

they were not truly basal, being obtained after only 20 min of recumbency. This perhaps is the reason for the differences (although not significant) in fasting mean serum HGH levels in the normals before the IVGTT and IVTTT. An earlier report by Pfeiffer (23) has reported higher levels of HGH in prediabetics compared to normals.

Our data indicate that there is a hypersecretion of HGH in prediabetics in response to tolbutamide. Furthermore, during the IVGTT 11 or 13 prediabetics showed an increase in HGH levels in response to the weak stimulus which is presumably caused by the decline of blood glucose during the intravenous glucose tolerance test (24); only 5 of 14 normal controls behaved similarly. It is of more than passing interest that the three prediabetics who exhibited the highest levels of serum HGH after tolbutamide (L. A., W. J., and B. D.) exhibited relatively high levels after intravenous glucose (59, 40, and 23 mμg/ml respectively at the 180 min interval; the highest, second highest, and fourth highest levels for this interval in the prediabetics). It seems reasonable to conclude from these results that the growth hormone–releasing mechanisms in prediabetics appear to be hyperresponsive to certain physiological stimuli.

It is unknown whether the overresponsiveness of the growth hormone–releasing mechanism in prediabetics is related to the malfunctioning of the β-cell. Also, it cannot be excluded that the HGH response might be a manifestation of another diabetogenic inborn error of metabolism.

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