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Research Article

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The Significance of Basal Insulin Levels in the Evaluation of the Insulin Response to Glucose in Diabetic and Nondiabetic Subjects *

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Abstract. The level of insulin after an overnight fast (basal) in 37 obese and nonobese male subjects with normal and abnormal carbohydrate tolerance was directly related to the increase in insulin concentration during a 3 hr 100 g oral glucose tolerance test. Obesity, but not diabetes, was associated with an elevation of this basal insulin level. Thus obesity predicted with the magnitude of the insulin response to glucose ingestion. When the individual insulin values were expressed as per cent change from the basal level, this effect of obesity was excluded. The insulin levels of all subjects with normal carbohydrate tolerance promptly rose 5–7-fold, and reached peak values 1 hr after oral glucose. In contrast, the diabetic response (as per cent increase) was markedly reduced during the 1st hr, and maximal (but still subnormal) insulin levels were not attained until 2 hr. In all subjects the insulin response (quantitated by calculation of the area circumscribed by a plot of the per cent change in insulin with time) showed a significant inverse correlation with the glucose response. Thus increasing degrees of carbohydrate intolerance were associated with decreasing insulin responses. Elevated levels of insulin, in both the basal state and in response to glucose, were related to obesity.

Introduction

When the first measurements of serum immunoreactive insulin levels were made during oral glucose tolerance tests (1), mild diabetics were observed to achieve higher insulin levels than subjects with normal glucose tolerance. Subsequently it was found that this exaggerated insulin response to glucose was not solely a feature of mild diabetes, but also occurred in obese nondiabetic subjects (2). The observation that weight reduction restored normal carbohydrate tolerance, and abolished the excessive insulin response to glucose in one obese, mildly diabetic subject, suggested that obesity may contribute to the high insulin levels found in mild diabetes (3).

Since most adult-onset diabetics are obese, the effect of obesity on insulin regulatory mechanisms must be carefully defined before insulin responses in diabetes can be properly evaluated. The present study was undertaken to separate the effects of obesity and diabetes on serum insulin responses to glucose.

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TABLE I

Blood glucose and serum insulin concentration during a 100 g glucose tolerance test

Subject	Age	Weight		Immunoreactive insulin Min:	*0	15	30	45	60	90	130	150	180	% IRI response	Blood glucose Min:	*0	15	30	45	60	90	120	150	180	Glucose response
	yr	*kg*	% ideal						*μU/ml*					*area units*						*mg/100 ml*					*area units*
Thin group																									
V.C.	51	65.8	96		17	44	71	130	121	61	60	50	30	296		67	81	99	111	97	68	67	52	48	391
M.W.	47	71.4	107		11	44	31	21	31	34	27	29	28	169		77	105	108	95	99	102	89	94	85	515
I.T.	48	92.6	113		11	49	71	79	96	56	26	16	12	322		71	106	134	124	123	107	90	63	48	526
T.T.	42	80.0	98		22	127	174	248	200	218	174	77	40	596		73	101	137	132	128	112	103	71	35	539
N.F.	55	75.4	112		15	74	96	62	67	69	78	34	45	315		76	106	127	119	112	107	102	82	96	549
E.T.	58	80.0	106		10	57	72	60	35	38	77	55	37	420		67	78	108	110	128	117	123	115	96	589
W.W.	41	55.6	90		9	41	63	48	95	86	86	86	49	700		76	95	117	127	142	114	86	104	103	589
J.C.	41	90.4	117		16	40	152	130	184	180	145	190	154	832		78	83	102	121	133	128	110	109	97	598
R.P.	47	84.8	105		8	60	24	42	42	48	36	56	33	427		74	113	101	136	146	139	105	117	93	634
B.O.	41	69.7	101		19	74	120	82	104	103	131	126	47	430		70	111	139	138	147	127	118	114	93	649
B.P.	50	66.8	103		13	28	62	56	97	127	114	73	59	532		75	85	116	140	165	174	120	98	93	670
L.L.	40	75.9	107		15	22	48	69	94	86	102	104	83	430		77	85	123	148	149	142	133	128	106	679
C.L.	51	66.8	94		23	45	56	74	109	90	117	92	56	264		82	104	128	158	169	153	132	118	109	713
E.M.	47	73.0	106		9	54	59	87	88	104	80	73	63	746		81	116	131	154	171	158	117	118	113	708
C.R.	52	63.7	80		19	44	46	86	104	101	124	92	154	395		92	93	107	91	134	149	143	130	137	678
D.O.	53	87.4	98		16	44	56	74	75	72	61	33	30	242		85	133	178	203	218	163	119	71	51	732
J.E.	48	64.5	101		20	18	40	78	74	78	95	48	40	208		71	89	128	152	173	180	185	114	64	744
H.P.	45	70.4	100		16	34	44	39	40	44	40	42	36	147		88	128	173	205	224	212	201	172	140	989
E.B.	47	70.9	100		8	21	28	16	15	45	40	39	36	291		127	142	159	154	177	222	249	270	270	1141
E.H.	49	70.4	110		16	8	4	5	14	18	34	22	25	141		176	190	192	196	226	279	304	309	303	1390
Obese group																									
W.M.	49	109.4	142		41	95	256	340	382	350	384	424	371	708		73	82	110	121	107	111	110	110	95	559
J.P.	44	145.4	172		45	87	120	146	160	165	172	154	130	220		65	75	90	108	118	140	122	101	93	585
H.T.	44	96.0	153		26	217	253	377	146	302	197	185	116	722		63	87	119	130	115	126	134	96	81	602
G.M.	53	106.3	141		33	69	218	298	325	125	145	168	106	423		73	99	128	151	136	114	111	106	96	607
O.C.	50	80.5	137		29	83	188	191	227	184	243	193	184	544		83	98	129	131	131	131	110	98	98	621
J.S.	50	99.0	135		23	47	120	178	236	132	228	157	173	594		66	77	119	142	149	151	121	107	107	650
J.J.	41	120.9	148		33	124	164	109	109	164	174	102	67	285		96	122	141	138	151	153	167	109	88	702
R.M.	42	113.8	135		29	44	90	60	60	82	80	80	60	142		105	106	131	121	124	134	150	155	117	704
W.N.	59	99.5	144		33	76	72	82	88	84	96	178	138	211		74	111	134	135	140	138	136	139	132	710
K.P.	60	81.0	128		17	52	64	73	119	135	107	112	54	458		71	106	142	162	188	168	162	117	72	745
A.M.	59	192.5	127		25	45	104	98	106	136	144	185	162	404		81	108	140	158	149	168	154	140	125	789
H.M.	44	100.4	130		41	93	152	186	212	224	244	194	84	343		88	124	173	199	198	180	152	115	96	800
A.H.	42	155.7	197		69	85	234	196	346	364	456	364	172	336		86	90	130	150	173	181	190	144	113	818
C.B.	41	131.5	174		35	79	55	62	74	78	126	116	123	159		102	128	130	130	152	172	188	178	165	855
M.G.	44	149.9	188		44	115	195	190	274	227	382	310	512	522		87	118	144	156	171	178	196	187	182	910
J.B.	42	116.2	164		88	114	176	238	352	367	372	366	329	245		100	120	144	183	202	206	193	181	174	949
R.C.	44	107.6	138		24	24	48	41	39	51	58	57	54	97		116	113	146	165	185	208	211	211	208	961

IRI, immunoreactive insulin.
* Mean of at least 2, usually 3, fasting samples.

Methods

37 (17 obese and 20 nonobese) ambulatory, apparently healthy male volunteers, aged 40 to 60, were studied. Of these, 34 subjects were hospitalized on a metabolic ward for 3 days before the study, and fed a weight-maintaining diet which contained 300 g of carbohydrate daily. The additional three subjects were hospital employees who received the same dietary preparation, but were not hospitalized. Seven subjects had previous evidence of carbohydrate intolerance and were receiving oral hypoglycemic treatment which was discontinued at least 1 wk before hospitalization for study. No subject had ever received insulin treatment. All subjects who weighed in excess of 25% of ideal body weight by Metropolitan Life Insurance Company tables were classified as obese; subjects who were within 15% of ideal body weight as nonobese.

After 3 days of dietary preparation in the hospital, 3-hr oral glucose tolerance tests (100 g glucose solution) were performed on all subjects at bed rest after an overnight fast. Two, and in most cases three blood specimens were obtained in the basal state via an indwelling needle before glucose ingestion. Additional blood samples were obtained at 15, 30, 45, 60, 90, 120, 150, and 180 min after glucose ingestion. Blood glucose was measured by glucose oxidase (4) and serum immunoreactive insulin (IRI) determined in duplicate by a modification of the double antibody technique of Morgan and Lazarow (5). In a representative assay, determination of the precision of replicate analysis (6) for 40 random unknowns yielded a coefficient of variation of 9.1%. At the conclusion of this study, one fasting serum sample from each subject was reanalyzed for insulin. The mean of these fasting samples was unchanged in the second assay. The coefficient of variation of these fasting insulin pairs determined in separate assays was 18%.

The mean area circumscribed by the blood glucose time curve was determined in duplicate by planimetry (glucose response), expressed in arbitrary units, and used as an index of glucose tolerance. This method quantitates the normal phenomenon of multiple blood glucose peaks, and therefore more closely reflects the total response to glucose ingestion (7). The insulin responses closely paralleled the changes in blood glucose, including the presence of more than one peak, and were also measured by planimetry and expressed in arbitrary units. To separate clearly normal from abnormal carbohydrate tolerance, we arbitrarily employed the mean glucose response of 10 normal nonobese subjects with no family history of diabetes as an index of normal glucose tolerance for all 37 subjects. Glucose responses that fell within one standard deviation of the mean response of the normal group were considered normal ($n = 14$), those between one and two standard deviations above the mean normal were considered "border-line" ($n = 10$), and those greater than two standard deviations above mean normal were considered diabetic ($n = 13$). The borderline subjects were excluded when the normal and diabetic insulin responses were separated and compared. However, all linear correlations include the responses of the entire group of 37 subjects. All data were punched on standard IBM cards and linear correlations determined by the use of BMD biomedical computer programs and the 7094 IBM computer (8). Areas were also determined by computer calculation (PDP 8) and agreed closely with those measured by planimetry.

Results

Fasting insulin levels of obese subjects (36 μU $\pm$ 17.6; mean $\pm$ SD) were significantly higher ($P < 0.001$) than those of the thin subjects (15 μU $\pm$ 4.8) (Table I). In the entire group of subjects, fasting IRI correlated directly with ideal body weight (Fig. 1, $r = 0.72$, $P < 0.001$), but not with glucose intolerance (Table II, $r = 0.25$,

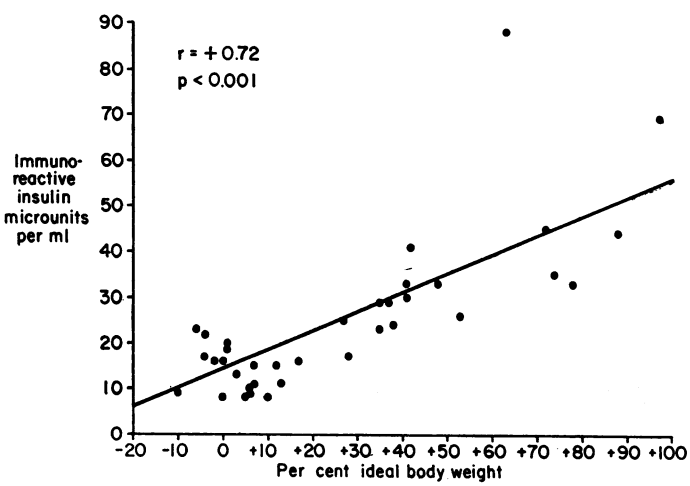

FIG. 1. CORRELATION OF FASTING SERUM IMMUNOREACTIVE INSULIN AND OBESITY EXPRESSED AS PER CENT OF IDEAL BODY WEIGHT.

TABLE II

*Correlation between insulin and glucose responses**

	Body weight % ideal	Fasting IRI	Fasting blood glucose	Glucose response	Insulin responses: 180 min per cent	60 min per cent	180 min absolute	60 min absolute
Body weight, % ideal		0.72	NS	NS	NS	NS	0.62	0.53
Fasting IRI	0.72		NS	NS	NS	NS	0.79	0.65
Fasting blood glucose	NS	NS		0.86	−0.45	−0.55	NS	NS
Glucose response	NS	NS	0.86		−0.40	−0.58	NS	NS
180 min IRI response (per cent)	NS	NS	NS	−0.40		0.61	0.51	0.60
60 min IRI response (per cent)	NS	NS	−0.55	−0.58	0.61		NS	0.68
180 min IRI response (absolute)	0.62	0.79	NS	NS	0.51	NS		0.85
60 min IRI response (absolute)	0.53	0.65	NS	NS	0.60	0.68	0.85	

IRI, immunoreactive insulin.
* r values are indicated where $P < 0.05$; NS = $P > 0.05$.

$P > 0.5$). Thus the degree of obesity, and not carbohydrate tolerance, was associated with the insulin level maintained after an overnight fast.

Insulin responses could not be evaluated without consideration of these fasting levels, since there was a highly significant linear correlation between fasting insulin and insulin response to glucose in both nondiabetic and diabetic subjects (Fig. 2). This indicates a tendency for subjects with higher fasting levels to demonstrate greater insulin responses to glucose. Of all measured variables, only obesity was associated with ele-

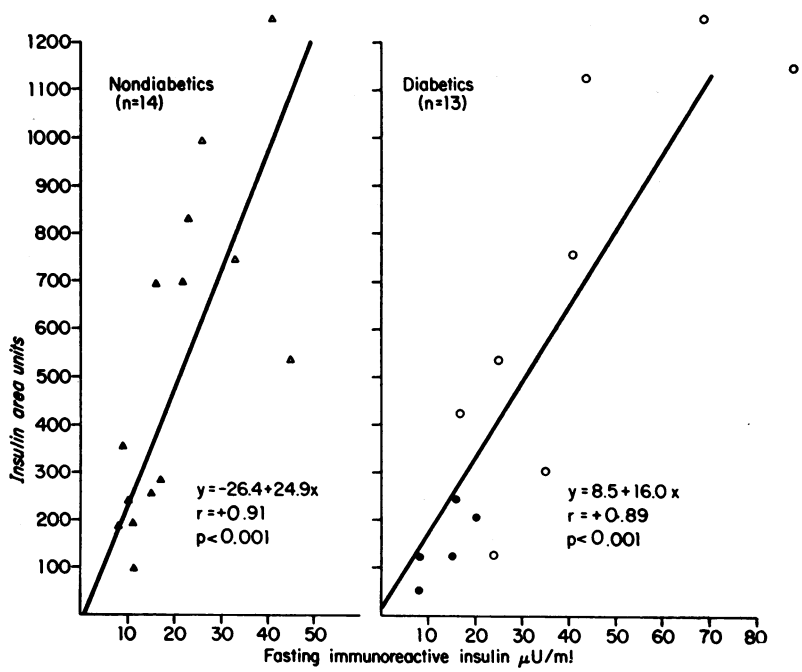

FIG. 2. RELATION BETWEEN FASTING INSULIN LEVELS AND THE ABSOLUTE AREA INCREMENT IN PLASMA INSULIN (TOTAL AREA MINUS FASTING AREA) IN THIN (▲, ●) AND OBESE (△, ○) NONDIABETIC AND DIABETIC SUBJECTS DURING 3-HR ORAL (100 G) GLUCOSE TOLERANCE TESTS.

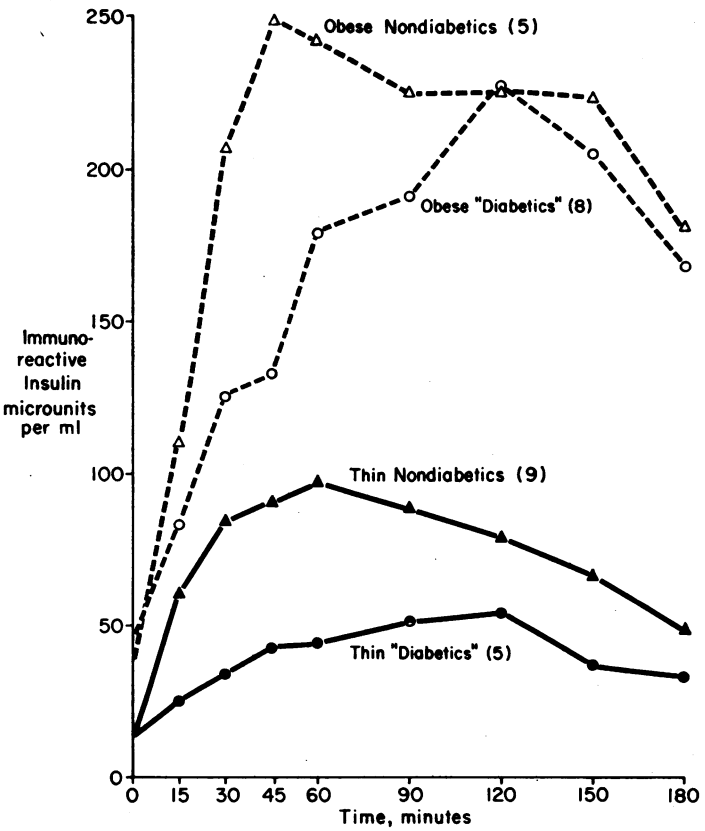

FIG. 3. THE MEAN ABSOLUTE INSULIN RESPONSES IN THIN AND OBESE NONDIABETIC AND DIABETIC SUBJECTS DURING 3-HR (100 G) ORAL GLUCOSE TOLERANCE TESTS.

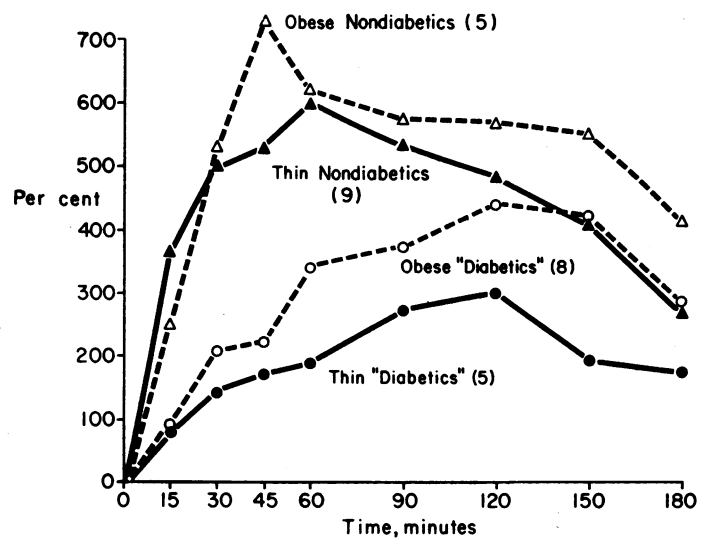

FIG. 4. INSULIN RESPONSES OF THIN AND OBESE NONDIABETIC AND DIABETIC SUBJECTS DURING 3-HR (100 G) ORAL GLUCOSE TOLERANCE TESTS EXPRESSED AS MEAN PER CENT INCREMENTS ABOVE FASTING LEVELS.

vated fasting insulin levels, and the insulin response to glucose was increased in both groups of obese subjects (Fig. 3).

This effect of obesity on insulin levels had to be eliminated to determine the relation between carbohydrate intolerance and insulin response. Two methods were tested. Responses were expressed as either a per cent change or an absolute increment above the fasting level. Only expression of the response as per cent changes ($r = -0.04$, $P > 1.0$) and not absolute increments ($r = 0.58$, $P < 0.001$) eliminated the correlation between obesity and insulin response.

When the insulin responses of all subjects were expressed in this way, thin and obese subjects with normal carbohydrate tolerance sustained a 5–7-fold elevation of circulating IRI levels within 60 min after glucose ingestion (Fig. 4). In contrast, diabetics did not achieve an early insulin peak, but reached maximum insulin levels at 2 hr. The insulin responses of the two nondiabetic groups were not significantly different from each other, and therefore the responses were averaged (Fig. 5). Similarly, the IRI responses of the two diabetic groups were not different, and also were averaged. When the nondiabetic and diabetic responses were grouped in this way, insulin responses were significantly decreased in diabetics at 15, 30, 45 ($P < 0.001$), 60 ($P < 0.01$), and 90 min ($P < 0.05$), but did not differ after 90 min. The area circumscribed by the 180 min integrated per cent insulin curve also was reduced in the diabetic subjects ($P < 0.05$). Thus the total insulin response to glucose was reduced in diabetes, and this impairment was most marked during the initial 90 min after glucose ingestion.

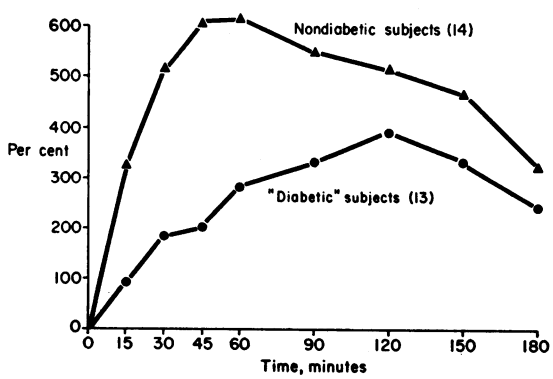

FIG. 5. INSULIN RESPONSES OF NONDIABETIC AND DIABETIC SUBJECTS EXPRESSED AS PER CENT CHANGES FROM FASTING LEVELS DURING 3-HR (100 G) ORAL GLUCOSE TOLERANCE TESTS.

This early impairment of insulin response to glucose in diabetes is emphasized by the highly significant inverse correlation of the glucose area and the 60 min integrated per cent insulin response in the entire group of 37 subjects (Fig. 6 A, $r = -0.63$, $P < 0.001$). However, a significant inverse correlation ($r = -0.46$, $P < 0.01$) was still present when the glucose and 180 min integrated per cent insulin responses were compared (Fig. 6 B). The assumption of a linear correlation was not necessary in this analysis, since the nonparametric rank-difference correlation test also showed a significant inverse correlation ($r = -0.41$, $P < 0.02$). Thus, progressively severe glucose intolerance appeared to be associated with decreasing insulin responses to glucose.

Discussion

The elevation of basal (fasting) insulin levels found in obese subjects is in accord with other recent observations (9–13). Since no prior attempts appear to have been made to correlate the fasting insulin level with the insulin response, the possibility that the fasting level might predict insulin responses has not been previously considered. Results in the present study show that insulin responses clearly are related to the fasting level.

The significant correlation of the degree of obesity and fasting insulin levels is extremely important, since some studies appear to indicate a relation between fasting insulin levels and diabetes (11, 12). However, when subjects with a wide range of glucose tolerance and body weight are examined, as in this study, only obesity and not carbohydrate intolerance is associated with elevated fasting insulin levels.

Although absolute insulin levels are probably important to peripheral tissues, they appear to be a poor index of the adequacy of an insulin response to a glucose stimulus. The relative increment above fasting levels and not the absolute level of circulating insulin appears to distinguish insulin responses in subjects with normal carbohydrate tolerance from insulin responses in subjects with abnormal carbohydrate tolerance. Thus when alterations in serum insulin levels are expressed as relative changes from the basal level,

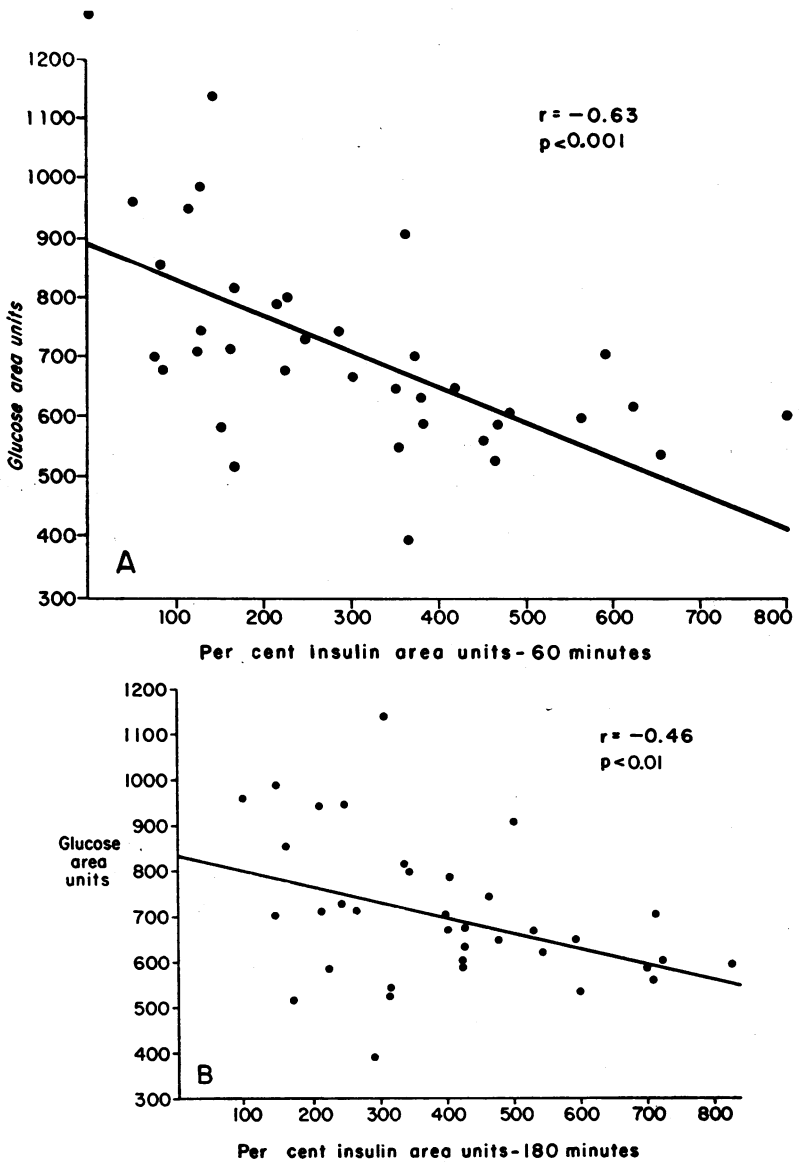

FIG. 6 A AND B. RELATION BETWEEN GLUCOSE TOLERANCE AND THE (A) 60 AND THE (B) 180 MIN INTEGRATED PER CENT INSULIN RESPONSE IN OBESE AND THIN NONDIABETIC AND DIABETIC SUBJECTS (n = 37).

both obese and thin nondiabetic subjects respond similarly.

Adiposity could theoretically influence both fasting insulin levels and the insulin levels in response to glucose by increasing tissue insulin requirements. In accord with this hypothesis, insulin sensitivity of human adipose tissue is diminished in obesity, both in the intact forearm preparation (9) and in isolated adipose cells (14). The observation that weight reduction results in both decreased insulin responses to glucose (3) and a decreased insulin requirement in diabetics further suggests that an increase in adipose tissue mass may impose a greater demand for insulin. If basal insulin levels influence the insulin response to glucose, then a diabetic insulin response may be greater than normal if this diabetic group includes subjects with higher basal insulin levels. The comparison of responses of groups of subjects with differing basal insulin levels may

explain the findings of elevated insulin levels in diabetes in several recent reports.

For example, a study of insulin levels in obesity (12) was interpreted to show that obese diabetics have greater insulin responses to glucose than obese nondiabetic subjects. Since the diabetic group had a higher mean fasting insulin level, the groups may not have been strictly comparable.

In another study (11) in which insulin levels in obese nondiabetic and diabetic subjects with identical mean fasting insulin levels were compared, the insulin response to glucose was reduced in the diabetic group. In contrast, in this same study the insulin response of the thin diabetic group appeared to be greater than normal. Since the mean fasting insulin level of the thin diabetic group was nearly twice that of the normal group, results of the present study would predict a greater insulin response.

In this study, obesity was the only factor which correlated with the fasting insulin level. It is clear, however, that per cent ideal body weight, which was employed to quantitate obesity, is a poor index of relative adiposity. Other factors, as yet unidentified, probably also influence basal insulin. In the present study two subjects with identical relative weights do not always have identical fasting insulin levels. Only when the group is examined as a whole does the relation between adiposity and basal insulin become evident. However a variation in insulin response related to differences in basal insulin, regardless of the cause, may be eliminated by normalization of the response.

Additional evidence has accumulated which supports the concept of impairment of insulin responses to a variety of stimuli in all diabetics, irrespective of weight. Insulin responses in mild diabetics have been found to be subnormal after the administration of both intravenous (15) and oral glucose (16, 17), a mixture of amino acids or arginine (17), and glucagon (18).

Although Yalow and Berson (19, 20) and Seltzer et al. (13) also noted a deficient early insulin response and late insulin peak in diabetes, some groups of mild diabetics in their series had greater than normal mean insulin responses to glucose independent of obesity. It is difficult to reconcile these results with the present observations. Differences in dietary preparation and patient selection may contribute to this apparent discrepancy.

If obesity is characterized by hyperinsulinism and carbohydrate intolerance by an insufficient insulin response, why do impaired carbohydrate tolerance and obesity so frequently coexist? Increased tissue demands for insulin in obesity appear to require a high output state of insulin release. If insulin secretory capacity is limited, the added stress on beta-cell reserve imposed by obesity may result in abnormal carbohydrate tolerance, even in the presence of elevated insulin levels.

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