A Familial Form of Obesity Without Hyperinsulinism at the Outset

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SUMMARY

A total of 32 pairs of obese fathers or mothers and their obese offsprings, aged 20 yr or younger, from 25 families with established hyperinsulinemic obesity was studied. Although the obese pairs with offsprings aged 11-20 yr equally showed an insulin hyperresponse to glucose, the offsprings 10 yr or younger revealed a rather normal insulin response, despite the presence of obesity, and this contrasted with their fathers or mothers. No difference was found in the estimated age of onset between the two groups of offspring. The offsprings in both age groups ate a similar high carbohydrate, high calorie diet.

The results suggest that the insulin hypersecretion is not the primary trait in this form of familial obesity and that the insulin response to glucose becomes augmented during the maturation years of 11–20, thus resulting in the accumulation of hyperinsulinemic and hyperlipidemic adults in the family. DIABETES *30*:14–18, January 1981.

Obesity is frequently associated with an exaggerated insulin response to glucose,[1,2] although this insulin hyperresponse is absent in certain forms of obesity.[3–5] In a series of family studies on adult subjects, we suggested that the above heterogeneity of insulin response in obesity originates from a familial basis.[6–8] Thus, hyperinsulinemic obesity, one specific form of obesity, tended to accumulate in families showing hyperlipidemia, hepatic steatosis, and possible secondary diabetes mellitus.[6,8,9] However, it was not clarified whether the insulin hypersecretion is inherited as the primary trait in this form of familial obesity, since obesity was shown to develop usually before maturation, but only a few juvenile offsprings of the hyperinsulinemic parents were examined.[6]

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We undertook this study to examine if there is a direct transmission of the increased insulin secretion from obese hyperinsulinemic fathers or mothers to their obese offsprings before maturation.

SUBJECTS AND METHODS

A total of 32 pairs of obese fathers or mothers and their obese offsprings aged 20 yr or younger was selected for this study from 25 families with hyperinsulinemic obesity, in which at least two first degree relatives of the index father or mother had obesity and hyperinsulinemia. The data on the adult relatives in 16 of the 25 families were published,[6,8] but the obese pairs with the young offsprings in these 16 families were examined independently in this study together with the obese pairs in nine new families. The subjects were judged obese when their relative weight (see footnote for Table 1) exceeded 120%. The insulin response of the parent group was regarded as abnormally high when the insulin sum during the oral glucose tolerance test (OGTT) exceeded the mean + 2 SD of the age-matched and sex-matched controls. Although several index fathers and mothers showed only high normal insulin levels (insulin sum: 200–300 μU/ml), they were also included in this study since their first degree relatives showed significant hyperinsulinemia. Thirty-two obese offsprings, aged 6–20 yr, consisted of 15 males and 17 females. The parent group, aged 29–51 yr, included 15 fathers and 14 mothers, in whom a father had two obese offsprings and a mother, three obese offsprings. The cases in which both parents were obese were not included in this study. None of the pair subjects showed the stigmata of other diseases or conditions of the endocrine-metabolic system. The nature of this investigation was fully explained to the participants. They were instructed to remain on their regular Japanese diet, and their weight was maintained stable. The dietary intake of the 32 obese offsprings, as well as the 12 nonobese offsprings, was recorded by their mothers during the 3 days before the examination, and their average daily intake was calculated.[10] A total of 81 healthy nonrelative subjects, including 38 subjects aged 5–20 yr and 43 subjects aged 29–50 yr, was

also examined as age-matched and sex-matched controls.

An OGTT, using 50 g of glucose, was performed after a 13–15 hour overnight fast. (In children aged under 10 yr, the standard dose of glucose used in the OGTT is 1.75 g/kg, but the children under 10 yr in the families of this study were all obese, weighing from 30 to 36 kg, and, therefore, we performed a 50 g OGTT in these subjects.) OGTT using 1.75 g/kg of glucose was performed in the control children aged under 10 yr. Venous and capillary (ear lobe) blood samples were obtained before and 30, 60, 90, and 120 min after the glucose loading. The fasting plasma samples were analyzed for triglyceride[11] (TG), total cholesterol[12] (TC), and patterns of lipoproteins with an agarose gel electrophoresis.[13] Blood glucose[14] and plasma insulin[15] were measured for the samples during OGTT.

Student's *t* test was applied to examine statistical significance.

RESULTS

Glucose or insulin sum in OGTT was used as an indicator of glucose tolerance or glucose-stimulated insulin secretion. The beta cell responsiveness to glucose was expressed as the insulinogenic index, the increment of plasma insulin above fasting level in μU/ml divided by the increment of blood glucose above fasting level in mg/100 ml at 30 min in OGTT. Since fasting blood glucose and plasma insulin levels were within normal limits in most obese pairs, those data were not analyzed independently. The obese pairs were divided into two groups: the one included the pairs with offsprings aged 10 yr or younger and the other included those with offsprings aged 11–20 yr. The control subjects were also divided into the premature group, the maturing group, and the adult group. The age range of the adult control group was equal to that in the fathers or mothers of the obese offsprings in both age groups.

The data on the control subjects are shown in Table 1. The glucose and insulin sums in the female controls of the age groups of 10 yr or younger and of 11–20 yr tended to be greater than those in the male controls, although the differences were not significant. No sex difference was noted in either the glucose sum or the insulin sum in the control subjects aged 31–50 yr.

The data on the two groups of the obese pairs are shown in Table 2. Relative weights in the offsprings of both age groups and their fathers or mothers were significantly greater than those in the controls. The male and female offpsrings of each age group tended to be more obese than their fathers or mothers, but the difference was not significant. The glucose tolerance was more or less impaired in the obese parent groups, and the glucose sum in the obese fathers with the offsprings aged 11–20 yr was significantly increased compared with that in the matched controls. Insulin sum as well as insulinogenic index increased significantly in the obese pairs with the offsprings aged 11–20 yr when compared with those in controls. However, the offsprings of both sexes aged 10 yr or younger showed levels of insulin sum and insulinogenic index within the normal range, as shown in Table 2, and this contrasted with their fathers or mothers as well as the offsprings aged 11–20 yr, in whom these levels elevated significantly compared with those in the matched controls.

Plasma TG increased significantly in the obese pairs compared with that in the controls, and the increase was greater in the males than in the females. Plasma TC level in the obese fathers with the offsprings aged 11–20 yr was also significantly higher than that in the controls, as shown in Table 2. The lipoprotein abnormalities in the obese pairs were judged mostly as type IV and occasionally as type IIb according to the agarose electrophoretogram and WHO phenotyping. None of the subjects showed the abnormality of broad beta disease.

Since the mean value and the standard deviation of each variable were approximately the same in both sexes in the controls of age range 31–50 yr, the variables including insulin sum and insulinogenic index were adjusted to the values corresponding to the above age group, according to the formula described previously.[6] Using the adjusted variables, a simple correlation analysis was performed in the obese pairs, as shown in Figure 1. There was no significant correlation in insulin sum between the pairs with the offsprings aged 10 yr or younger. However, a significant positive correlation ($r = 0.72$) existed in insulin sum between the pairs with the offsprings aged 11–20 yr. There were no significant correlations in the insulinogenic index between

TABLE 1
Clinical and laboratory data of controls

Age range	Sex	Age (yr)	Relative weight (%)	Glucose sum (mg/100 ml)	Insulin sum (μU/ml)	Insulinogenic index	Triglyceride (mg/100 ml)	Total cholesterol (mg/100 ml)
≤10 yr	M (N = 9)	8 ± 1	99 ± 2	571 ± 10	154 ± 25	0.58 ± 0.10	58 ± 6	164 ± 7
	F (N = 6)	9 ± 1	98 ± 4	596 ± 25	168 ± 37	0.49 ± 0.11	49 ± 4	164 ± 13
11–20 yr	M (N = 13)	16 ± 1	97 ± 3	509 ± 16	176 ± 16	0.83 ± 0.09	69 ± 5	178 ± 7
	F (N = 10)	16 ± 1	101 ± 5	544 ± 16	181 ± 21	0.84 ± 0.11	53 ± 9	159 ± 11
31–50 yr	M (N = 25)	41 ± 2	109 ± 3	540 ± 12	173 ± 12	0.74 ± 0.09	92 ± 8	188 ± 6
	F (N = 18)	39 ± 2	111 ± 4	555 ± 20	175 ± 16	0.72 ± 0.08	76 ± 7	198 ± 6

Mean values ± SE are shown. Relative weight: (actual weight/standard weight) × 100 (%). Standard weight: (height in cm − 100) × 0.9 (kg). Glucose or insulin sum: sum of five blood glucose or plasma insulin values during oral glucose tolerance test. Insulinogenic index: increment of insulin in μU/ml divided by increment of glucose in mg/100 ml at 30 min after glucose loading.

TABLE 2
Clinical and laboratory data of obese pairs

	Age (yr)	Relative weight (%)	Glucose sum (mg/100 ml)	Insulin sum (μU/ml)	Insulinogenic index	Triglyceride (mg/100 ml)	Total cholesterol (mg/100 ml)
Obese pairs (offsprings: 10 yr or younger)							
Offsprings							
M (N = 6)	8 ± 1	152 ± 9*	549 ± 17	162 ± 33	0.56 ± 0.26	134 ± 36*	162 ± 10
F (N = 8)	8 ± 1	160 ± 8*	546 ± 26	188 ± 37	0.66 ± 0.14	128 ± 19*	166 ± 8
Fathers (N = 8)	38 ± 1	134 ± 3*	609 ± 35	304 ± 39*	1.53 ± 0.28*	304 ± 112*	209 ± 8
Mothers (N = 6)	33 ± 2	136 ± 6*	673 ± 52	388 ± 28*	1.47 ± 0.16*	160 ± 28*	204 ± 19
Obese pairs (offsprings: 11–20 yr)							
Offsprings							
M (N = 9)	14 ± 1	148 ± 7*	590 ± 37	347 ± 59*	1.83 ± 0.52*	197 ± 41*	176 ± 15
F (N = 9)	16 ± 1	145 ± 7*	608 ± 55	339 ± 61*	1.69 ± 0.31*	127 ± 27*	170 ± 12
Fathers (N = 7)†	47 ± 4	132 ± 3*	715 ± 20*	357 ± 43*	1.17 ± 0.13*	291 ± 56*	232 ± 8*
Mothers (N = 8)†	43 ± 2	140 ± 5*	595 ± 24	362 ± 33*	1.62 ± 0.36*	150 ± 27*	211 ± 11

Mean values ± SE are shown. Annotations for the variables are similar to those in the footnotes for Table 1.
* Significantly ($P < 0.05$) increased compared with the age-matched and sex-matched control values in Table 1.
† One father had 2 obese offsprings and one mother 3 obese offsprings.

the pairs either with the offsprings aged 10 yr or younger ($r = 0.16$) or with the offsprings aged 11–20 yr ($r = 0.13$).

Each family including two or more obese offsprings was further analyzed to compare the insulin response and other variables between the offsprings with similar genetic disposition who were in different age groups. The data of such families are shown in Table 3. In family 4, a mother had three offsprings, and in family 11, a father had two offsprings. However, the age range of these obese siblings was too narrow to see the possible age relation of the variables. In families 1, 9, 10, and 12, the age-related change in the insulin response was noted among the obese offsprings (mostly cousins). In these families, the insulin sums in the offsprings aged 10 yr or younger remained within normal limits in contrast to the elevation in the offsprings aged 11–20 yr. The mean insulin sum in the offsprings aged 10 yr or younger was about a half that in the offsprings aged 11–20 yr, the difference being statistically significant, as shown in Table 3. In these families, the insulinogenic index also tended to remain normal in the offsprings aged 10 yr or younger, and it increased variably and insignificantly in the offsprings aged 11–20 yr. No significant difference was noted between the offsprings of the two age groups of these families in relative weight, glucose sum, TG, or TC.

An analysis of the past history on body weight revealed that the offsprings aged 10 yr or younger and those aged 11–20 yr had become obese at the age of 5.6 ± 0.4 yr (mean ± SE) and of 7.3 ± 0.9 yr, respectively, the difference being not significant. The diet analysis revealed the total calorie consumptions to be 2054 ± 51 kcal/day in the 14 obese offsprings aged 10 yr or younger, 2112 ± 97 kcal/day in the 18 obese offsprings aged 11–20 yr, and 1886 ± 50 kcal/day in the 12 nonobese control offsprings aged 10–20 yr. The daily carbohydrate intakes were 318 ± 18 g in the offsprings aged 10 yr or younger, 302 ± 24 g in the offsprings aged 11–20 yr, and 287 ± 24 g in the nonobese offsprings. The calorie intake in the obese offsprings of either age group was significantly ($P < 0.05$) higher than that in the nonobese offsprings, although the difference in the calorie intake between the obese offsprings of both age groups was not significant. No significant difference was found in the carbohydrate intake between the obese and nonobese offsprings.

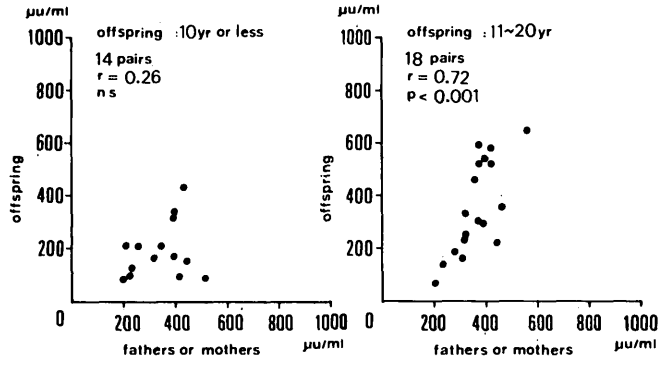

Figure 1. Correlation of insulin (sum of five plasma insulin values in oral glucose tolerance test) between the pairs of obese fathers or mothers and their obese offsprings. The correlation is not significant between the pairs with the offpsrings aged 10 yr or younger (left panel) and it is significant ($P < 0.001$) between the pairs with the offsprings aged 11–20 yr (right panel).

DISCUSSION

Most obese pairs similarly showed the insulin hypersecretion with a slightly impaired glucose tolerance. However, of importance seems to be the finding that the obese offsprings aged 10 yr or younger revealed rather normal insulin levels, which is in contrast to the elevation in their fathers or mothers and in the offsprings aged 11–20 yr. No sex difference was found in the insulin response of the offsprings. Despite the presence of obesity, the insulin response in each of the premature offsprings aged 10 yr or younger did not resemble that in his or her father or mother, as indicated by correlation analysis, and this is a different finding from that in the pairs wtih the offsprings aged 11–20 yr. The insu-

TABLE 3
Clinical and laboratory data in the families with plural obese offsprings

Family no.		Age (yr)	Relative weight (%)	Glucose sum (mg/100 ml)	Insulin sum (μU/ml)	Insulinogenic index	Triglyceride (mg/100 ml)	Total cholesterol (mg/100 ml)
1	Mother	47	152	620	388	2.15	98	184
	Son	12	148	521	293	1.11	123	184
	Mother	32	140	602	412	1.50	118	212
	Son	6	138	552	89	0.20	131	158
4	Mother	41	132	511	374	1.25	220	236
	Son	17	151	552	299	1.43	107	219
	Daughter	15	189	1005	589	2.75	173	209
	Son	13	198	488	520	4.98	251	217
9	Mother	48	139	684	465	0.61	182	228
	Son	19	140	682	351	1.12	121	138
	Father	42	154	620	512	2.90	153	194
	Daughter	6	153	490	83	0.64	106	148
10	Father	51	138	811	559	1.58	263	240
	Daughter	15	158	592	647	2.83	252	225
	Mother	29	144	585	258	1.65	256	282
	Son	8	160	502	181	0.13	118	167
11	Father	42	125	727	419	1.13	515	200
	Son	16	130	718	578	1.45	235	195
	Son	14	124	705	518	2.93	359	180
12	Father	35	146	665	235	1.65	310	261
	Son	12	162	488	182	0.22	97	117
	Father	37	128	518	228	1.69	153	202
	Daughter	10	168	510	125	0.93	95	157
(Families 1, 9, 10, 12)								
Offsprings ≤ 10 yr								
	Mean	8*	155	514	120*	0.48	113	158
	SE	1	7	14	23	0.19	8	4
Offsprings 11–20 yr								
	Mean	15	152	571	368	1.32	148	166
	SE	2	5	43	99	0.55	35	24

* Significantly ($P < 0.05$) different from the value in the offsprings aged 11–20 yr. Annotations for the variables are similar to those in the footnotes for Table 1.

linogenic index in the premature offsprings of both sexes was not enhanced, suggesting normal glucoreceptor activity of the beta cells at this stage. However, in the maturing male and female offsprings aged 11–20 yr, the index increased variably.

There was no significant difference between the offsprings of the two age groups in the onset of their overweight or in their relative polyphagia as estimated in this study. Since the obese offsprings in both age groups were all selected from families with established hyperinsulinemic obesity, the genetic homogeneity for obesity seems to exist in the offsprings studied. To rule out family differences, analysis of each family with offsprings in both age groups was performed, and the results indicated that the insulin response in the obese offsprings aged 10 yr or younger still remained within the normal range, while their obese relatives aged 11–20 yr showed an exaggerated insulin response to glucose.

Thus, while it is possible that this form of obesity is commonly associated with excessive calorie intake, the insulin response to glucose is not uniform and appears to alter during the maturation process of years 11 through 20, thus leading normoinsulinemic infants to hyperinsulinemic adults. The pathophysiology of obesity is heterogeneous,[16] and, generally, hyperinsulinemia is not characteristic of the infantile hyperplastic obesity while it is common in the adult hypertrophic obesity.[4,5] Although we did not estimate the adipose tissue cellularity, it is possible that the major cellularity typing can be changed during the periods of 11–20 yr. Even though a longitudinal study is obviously warranted to establish the process, it is highly likely that the insulin secretory function is not the primary trait in this familial hyperinsulinemic obesity and that insulin is playing no important role in the initial weight gain. The insulin hypersecretion seems to become manifest during growth and maturation under some genetic influences in both sexes, accelerating the lipid disorders, as shown in this study.

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