

Correlative Studies in Obese Children and Adolescents Concerning Body Composition and Plasma Insulin and Growth Hormone Levels

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Extract

Levels of plasma insulin, growth hormone (HGH), glucose, and free fatty acids (FFA) were investigated in 17 obese, nondiabetic children or adolescents after administration of intravenous arginine, oral glucose, and a protein-glucose meal. These results were compared with those obtained in eight normal adolescents. Four of the obese patients had a family history of diabetes but had hormonal responses identical with those observed in obese subjects with a negative family history of diabetes. Subjects were arbitrarily separated into two groups depending on duration of obesity (Table I) (age of onset was different: infancy or early childhood for *group B*, 5-8 years for *group A*). Subjects in *group B* (longstanding obesity) all had a strong family history of obesity with marked increases in body weight, body fat, and excess fat. Fasting levels of insulin were greater than normal ($P < 0.001$ (Table II)). Patients in *group A* (short duration), with lesser increments in body weight and body fat, had normal fasting levels of insulin and normal response to intravenous arginine (Fig. 4). All obese subjects had hyperinsulinemia in response to other stimuli, but patients in *group B* achieved the highest insulin levels (Figs. 2, 3, and 4). All obese patients had significantly decreased levels of HGH during tests and elevated fasting levels of FFA. Patients in *group B* exhibited a reduced mean decrement in FFA during the oral glucose tolerance test.

Whether or not responses seen in patients in *group A* represent an early stage of the conditions observed in patients in *group B* cannot be determined by this study, but the biochemical changes reported in established obesity of childhood mimic those found in the adult.

Speculation

Obesity in children is associated with excess lipogenesis and hyperinsulinemia, which are interdependent and initiated through maximal nutritional intake in infancy.

Eventually muscle becomes resistant to insulin with decreased transport of glucose into the cell and decreased protein synthesis relative to DNA. The reduced levels of growth hormone in the circulation may indicate excessive uptake by muscle, which is followed, in some instances, by an associated proliferation of nuclei.

Introduction

The problem of obesity has recently been reviewed [3, 12, 19, 23, 41].

In contrast with the voluminous data concerning hormonal abnormalities in the obese adult [4, 27, 28, 32, 35, 37], relatively little is known about the magnitude of such abnormalities in obese children or adolescents [11, 33].

Previous investigators [2] have reported a correlation between total body weight and fasting levels of insulin in obese adults; others, however, have been unable to demonstrate a correlation between fasting levels of insulin and total body fat in obese adolescents [11, 15].

One problem has been the inability to assess normal or expected fatness in children and the degree of excess fatness in obese children. Mellits and Cheek [30] have constructed quadratic equations using data on body water and length (in centimeters) to predict "expected body fat" in the normal male and female from childhood to 30 years.

In a previous publication [10], children and adolescents with obesity were studied with respect to body composition. It was possible to inspect lean body mass, fat mass, and excess fat as well as changes in muscle and adipose tissue.

The present study was undertaken in an attempt to determine the levels of insulin and growth hormone in these same patients and to seek relationships of these hormones with body fat and body composition.

Materials and Methods

Seventeen obese individuals (five males and 12 females), 6.9–17.7 years of age, were selected as voluntary subjects for these studies. Body weights ranged from 47.6–179.2 kg and all weights were clearly above the 97th percentile. Eight healthy nonobese youngsters (six males and two females, ranging from 9 to 18 years of age) served as a normal control group. None of the patients had received any therapy previously for their obesity. None of the patients had diabetes mellitus at the time of testing, although four patients (019, 056, 057, and 060) had a family history of diabetes in either a maternal grandparent or maternal aunt.

Each subject under study was placed on a diet providing at least 250 g carbohydrate daily for at least 4 days prior to admission. Studies were performed in the Pediatric Clinical Research Unit of the Johns Hopkins Hospital over a period of 6 days.

The following tests were performed on separate days

following an overnight fast. Oral glucose tolerance test: 1.75 g glucose/kg actual body weight to a maximum of 100 g. Glucose was given as a 50% solution in water. Thus, the heavier patients tested (*group B*) received a smaller dose of glucose per kilogram of body weight than did subjects in *group A*. Protein-glucose meal: 1 g beef protein/kg body weight in the form of steak or hamburger was ingested simultaneously with a dose of glucose equal to that received during the oral glucose tolerance test. Arginine tolerance test: 0.5 g L-arginine monohydrochloride [45] per kilogram actual body weight to a maximum of 40 g. The arginine was administered intravenously as a 10% aqueous solution over a period of 30 min. Since an arbitrary maximum of 40 g was administered, the patients in *group B* received a smaller dose of arginine per kilogram of body weight than did those in *group A*.

All blood specimens were collected from indwelling nonheparinized needles placed in the antecubital or dorsal hand vein. Samples were collected into heparinized glass test tubes and immediately centrifuged, and the plasma was separated and kept frozen at -4° for later analysis. Blood specimens were obtained at -15 , 0, 30, 60, 90, 120, 240, and 300 min during the oral glucose tolerance test and at -15 , 0¹, 0², 30, 60, 90, 120, 180, 240, and 300 min during the protein-glucose meal. Time 0¹ indicates the time at which the meal was begun and time 0² when the meal was completed. The time required for ingestion of the test meal varied between 15 and 20 min in all of the subjects. All subsequent times for sampling represent the time elapsed since completion of the meal.

During the arginine tolerance test blood was drawn at -15 , 0, 20, 30, 45, 60, 90, and 120 min after the start of the infusion.

All determinations were performed on plasma samples. Glucose was determined by a glucose oxidase method [31] and free fatty acids (FFA) by the Dole method [13] as modified by Trout, Estes, and Friedberg [12]. Immunoreactive insulin (IRI) was assayed by the radioimmunoassay method of Yalow and Berson [44] with a slight modification [24]. Immunoreactive growth hormone (IGH) was assayed by a radioimmunoassay technique of Schalch and Parker [39]. All plasma specimens for glucose and FFA were assayed in triplicate and for IRI and IGH in duplicate. All of these data are expressed in the text or figures as the mean \pm standard error of the estimate.

Deuterium space was used for determination of total body water (TW) and corrected bromide space for extracellular volume (ECV) [5]. Lean body mass (LBM)

and total body fat (TBF) were determined by the use of the Pace constant (0.72) [1, 10]. Thus LBM and TBF may be determined from the following equation:

$$\text{LBM} = \frac{\text{TW}}{0.72}$$

It follows that: TBF = body weight - LBM.

Expected body fat was also predicted from height according to the following equations [30]:

For 145 males, fat (kg) = 12.116 - 0.215 (ht) + 0.00114 (ht)², SD = 3.84

For 74 females, fat (kg) = 27.514 - 0.538 (ht) + 0.00279 (ht)², SD = 3.43

For the obese individual it is possible to assess body fat from body water [1, 10] and subtract "expected fat" to obtain "excess fat." The identifying code numbers are the same as those employed in a previous communication [10] which describes in detail the body composition of these subjects.

Results

The obese subjects were divided into two groups based on duration of obesity, which was determined in all subjects either by annual weight records or family pictures. Subjects in *group A* became obese at approximately 5-8 years of age and the duration ranged from 2 to 4.5 years at the time of study. Subjects in *group B* became clinically obese either in infancy or very early childhood, but always prior to 5 years of age. The duration of obesity ranged from 6.5 to 15 years. This division was maintained during analysis of certain data to determine whether duration of obesity, irrespective of age of onset, influenced hormonal patterns. Table I summarizes the clinical data of the subjects studied.

All obese subjects in both groups were well over the 97th percentile for weight. No attempt was made to analyze critically the differences in heights of the groups because of the considerable differences in age at the time of study. There was a striking preponderance of obese family members among those in *group B* in contrast to those in *group A*.

Table I. Clinical data

	Code no.	Age, yr	Sex	Height		Weight		Family history of obesity ¹	Age onset of obesity, yr	Duration of obesity, yr
				cm	percentile	kg	percentile			
Normal group	N-61	15.2	M	181.4	97	78.6	97	S		
	N-62	15.8	M	187.0	>97	76.5	97	Negative		
	N-63	17.5	M	171.9	25	59.3	25	Negative		
	G-3	11.0	M	148.7	75	41.5	75	B		
	G-6	14.3	M	165.0	50	52.1	50	S		
	PR	8.9	M	148.7	>97	37.7	90	Negative		
	N-60	18.0	F	160.0	25	51.1	25	S		
	JR	12.3	F	168.1	>97	48.6	75	Negative		
Obese group A	053	9.3	M	141.0	75	55.0	>97	F, M, B	6-7	3
	041	10.0	F	152.0	97	62.7	>97	Negative	7-8	3
	050	6.9	F	129.5	90	47.5	>97	Negative	5-6	2
	055	11.8	F	150.5	50	63.2	>97	Negative	7-8	4.5
	062	11.0	F	145.0	50	60.3	>97	Negative	8-9	3
Obese group B	047	16.7	M	185.4	97	196.3	>97	F, B	2-3	14.5
	051	14.2	M	172.7	90	109.1	>97	F, B	3-4	11
	054	14.2	M	171.5	90	96.4	>97	F, M, B	3-4	11
	063	17.7	M	182.2	90	160.0	>97	GF, GM, A, U	3-4	14.5
	049	13.1	F	164.0	90	76.4	>97	GF, GM	4-5	9
	052	10.7	F	148.6	75	66.0	>97	F	4-5	6.5
	056	9.5	F	137.8	75	64.9	>97	M, GF, GM, A	2-3	7.5
	057	17.0	F	154.9	10	109.2	>97	M, GF, GM, A	2-3	15
	058	9.2	F	154.8	>97	62.7	>97	M	1-2	8
	059	12.1	F	154.0	75	77.9	>97	GF, GM, A, U	2-3	10
	060	13.5	F	165.0	90	127.5	>97	F, M	3-4	10
	061	14.1	F	160.0	50	98.4	>97	GF, GM, A	2-3	12

¹ F: Father. M: Mother. B: Brother. S: Sister. GF: Grandfather. GM: Grandmother. A, U: Aunt or Uncle.

Table II. Biochemical data

	Code no.	ECV, liters	Fasting IRI, ¹ μ U/ml	Protein-glucose meal peak IRI, ¹ μ U/ml	Weight, kg	TBF ² , kg	TBF, % body wt	Excess fat, ³ kg	Excess fat, % body wt	LBM, kg
Normal group	N-61	17.37	20.4	174.0	78.6	18.5		0.0		60.1
	N-62	18.49	22.0	211.0	76.5	13.0		0.0		63.5
	N-63	14.10	24.7	280.0	59.3	7.9		0.0		51.4
	G-3	9.43	17.8	134.0	41.5	5.5		0.0		36.0
	G-6	11.92	20.1	52.0	52.1	N.A. ⁴		N.A.		N.A.
	PR	N.A.	23.6	76.0	37.7	N.A.		N.A.		N.A.
	N-60	10.87	15.2	260.0	51.1	12.0		0.0		39.1
	JR	N.A.	21.0	105.0	48.6	N.A.		N.A.		N.A.
Obese group A	053	11.09	14.0	217.0	55.0	19.7	36	15.2	27.5	35.3
	041	10.81	4.7	234.0	62.7	28.7	46	18.4	29.0	34.0
	050	8.14	19.8	173.0	47.5	14.5	30.5	9.8	21.0	33.0
	055		25.1	224.0	63.2	29.3	46	19.6	31.0	33.9
	062	11.41	20.7	266.0	60.3	22.3	37	10.7	18.0	38.0
Obese group B	047	35.12	44.1	520.0	196.3	100.7	51	89.2	45.0	95.6
	051	N.A.	49.8	1120.0	109.1	N.A.		N.A.		N.A.
	054	13.19	40.5	824.0	96.4	36.9	38	28.1	29.0	59.5
	063	28.12	38.5	328.0	160.0	93.4	58	82.6	52.0	66.6
	049	17.24	44.0	384.0	76.4	34.5	45	20.1	26.0	41.9
	052	11.69	35.5	540.0	66.0	25.3	38	16.1	24.0	40.7
	056	11.13	46.5	872.0	64.9	24.1	37	17.7	27.0	40.8
	057	17.24	45.0	600.0	109.2	56.6	52	45.5	42.0	52.6
	058	11.10	30.1	276.0	72.7	20.0	32	9.0	14.5	42.7
	059	11.12	39.8	680.0	77.9	36.3	46.5	25.5	33.0	41.6
	060	20.63	53.5	N.A.	127.5	50.3	39.5	35.6	28.0	77.2
	061	15.28	32.4	344.0	98.4	40.9	41.5	28.0	28.5	57.6

¹ IRI: Immunoactive insulin. TBF: Total body fat. LBM: Lean body mass.

² TBF: Body weight - LBM.

³ Excess fat = actual body fat - predicted body fat [30].

⁴ N.A.: Data not available.

Body Fat and Excess Fat

Data on body weight, body fat, and excess fat are recorded in Table II. The older the patient, the heavier the patient and the greater the body fat. Accordingly, excess fatness increased with time. Body weight, body fat, and excess fat are, of course, greatly in excess for age or body length by comparison with normal children; however, body fat expressed as a percentage of body weight yields values for *group A* of 30-46 and for *group B* of 32-58. An overlap exists.

Fasting Plasma IRI Levels and Circulating Insulin

The levels for IRI are presented in Table II. The fasting levels of IRI in each subject represent the mean value of six samples obtained after six consecutive overnight fasts.

The fasting level of insulin in the normal group was 20.6 ± 2.7 μ U/ml and 16.9 ± 3.4 and 41.6 ± 1.9 μ U/ml in obese *groups A* and *B*, respectively. The

difference between normal subjects and those in *group A* was not significant. The values were significantly different, however, between those in obese *group B* and the normal group ($P < 0.001$) and between both obese groups ($P < 0.001$).

An increasing ratio of fat to body weight did not correlate with the fasting insulin level; nevertheless, the extra fat in terms of absolute amounts appeared to hold some relation with the levels of fasting insulin. If a rough measure of the circulating insulin is obtained by multiplying plasma concentration of insulin by extracellular volume [14] then the correlation of this determinant against "excess fat" is found to be high ($r = 0.92$). Moreover, if circulating insulin is considered in relation to total body fat or excess fat as a percentage of body weight, the correlation is still reasonable ($r = 0.70$). Thus the degree of fatness or excess fat would appear to be associated with the amount of circulating insulin. Although the fasting concentration of insulin was higher in patients of *group B* but did not corre-

late with fat as a percentage of body weight, it appeared that the longer the duration of obesity, the higher the level of fasting insulin (Fig. 1).

Plasma Insulin and the Response to Glucose and Protein

The values for IRI during the oral glucose tolerance test are shown in Figure 2. Obese group A had levels of IRI significantly higher than those found in the normal group at 30 and 180 min ($P < 0.005$ and < 0.05) Obese group B achieved levels of IRI greater than those seen in the normal group at 30, 90, 120, and 180 min ($P < 0.02$, < 0.05 , < 0.05 , and < 0.005). All three groups had their peak IRI responses at 30 min.

The responses to the protein-glucose meal are presented in Figure 3. Obese group A showed significantly higher levels of IRI than did those in the normal group at only time 0² ($P < 0.02$). The values for IRI were significantly different, however, between obese group B and the normal group throughout the entire test (P range between < 0.02 and < 0.001), and between both obese groups at 30, 60, 90, 120, 180, and 300 min (P range between < 0.05 and < 0.005). The peak responses of IRI were achieved at 30 min in all three groups.

During the arginine tolerance test obese group A had levels of IRI not significantly different from normal subjects (Fig. 4). Obese group B, however, had values for IRI significantly higher than that found in the normal group at 15, 30, 45, 60, and 90 min ($P < 0.005$, < 0.005 , < 0.005 , < 0.05 , and < 0.01) and higher than that found in obese group A at 30, 45, and

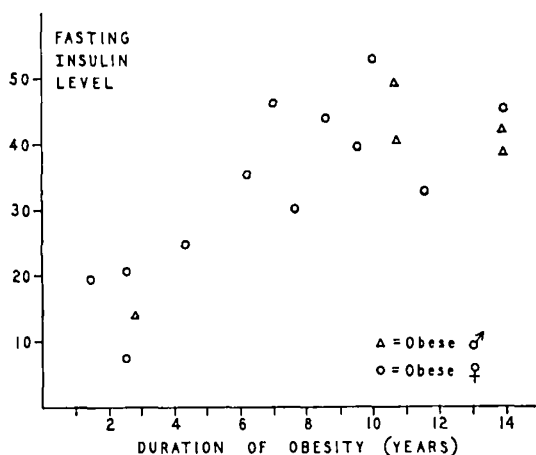


Fig. 1. Relationship between duration of obesity (years) and fasting plasma immunoreactive insulin levels as conventionally expressed in microunits per milliliter. The points appear to rise progressively.

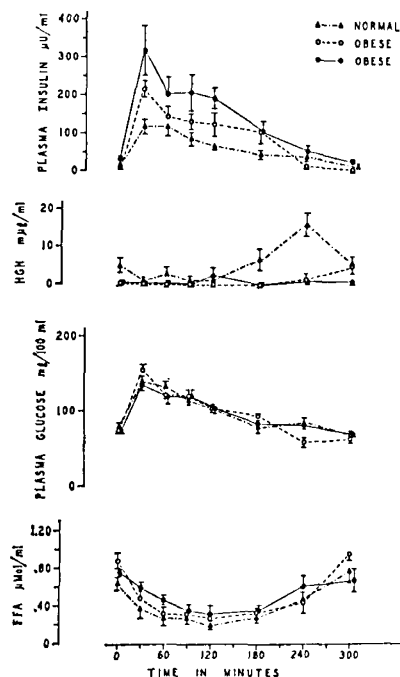


Fig. 2. Oral glucose tolerance test. Plasma levels of insulin, growth hormone (GHG), glucose, and free fatty acids (FFA) in the groups studied. The values represent mean \pm SEM.

90 min ($P < 0.05$, < 0.02 , and < 0.05). Once again, the three groups reached peak values of IRI at 30 min.

Plasma Growth Hormone (GHG) Levels

The mean fasting value in the normal groups was 3.6 ± 0.9 m μ g/ml, compared with 0.5 ± 0.2 and 0.3 ± 0.1 m μ g/ml in obese groups A and B, respectively. The differences were significant between normal subjects and those in group A ($P < 0.005$) and between normal subjects and those in group B ($P < 0.001$) but not between both obese groups.

The values for GHG in the normal group during the oral glucose tolerance test were significantly higher than those seen in obese group A at 180 and 240 min ($P < 0.05$ and < 0.05) and higher than that observed in obese group B at 240 and 300 min ($P < 0.02$ and < 0.05). The level of GHG at 300 min was significantly greater in obese group A than that in B ($P < 0.05$) (Fig. 2). The mean peak response of GHG was 15.2 ± 2.6 m μ g/ml in the normal group compared with 5.7 ± 1.5 m μ g/ml in obese group A ($P < 0.01$) and 3.9 ± 1.6 m μ g/ml in obese group B ($P < 0.005$). The differences between both obese groups were not significant.

In response to arginine stimulation (Fig. 4) the normal group had values for GHG that were significantly higher than those seen in obese group A or B at 60 and

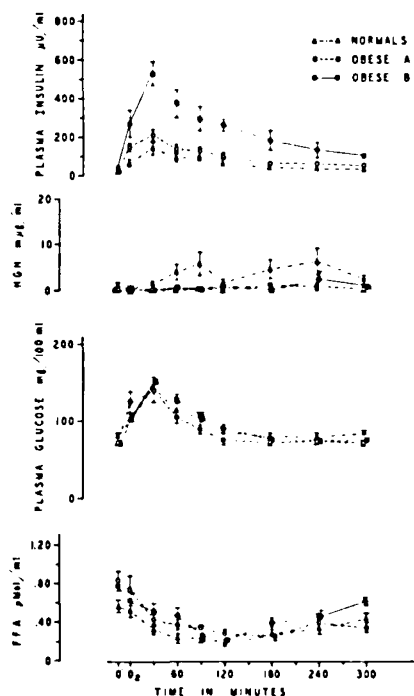


Fig. 3. Protein-glucose meal. Plasma levels of insulin, growth hormone (GHG), glucose, and free fatty acids (FFA) in the groups studied. The values represent mean \pm SEM. The significant differences referred to in the text are valid although the figure does not appear to reflect these differences accurately.

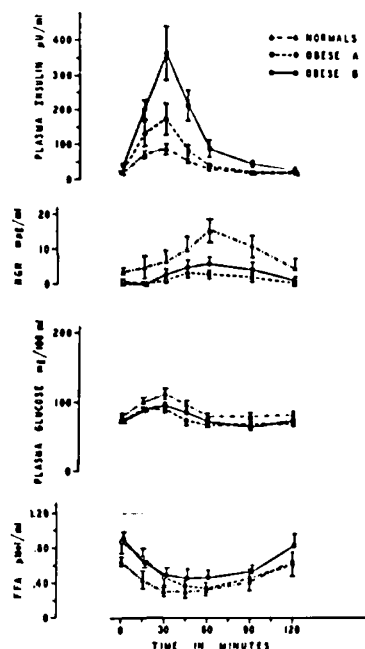


Fig. 4. Arginine tolerance test. Plasma levels of insulin, growth hormone (GHG), glucose, and free fatty acids (FFA) in the groups studied. The values represent mean \pm SEM. The significant differences referred to in the text are valid although the figure does not appear to reflect these differences accurately.

90 min ($P < 0.05$ and < 0.05). The mean peak response for GHG was 15.4 ± 3.7 $\text{m}\mu\text{g}/\text{ml}$ in the normal group, 4.1 ± 1.3 $\text{m}\mu\text{g}/\text{ml}$ in obese group A ($P < 0.025$), and 6.5 ± 2.2 $\text{m}\mu\text{g}/\text{ml}$ in obese group B ($P < 0.05$). The differences between both obese groups were not significant.

Plasma Glucose

The fasting level of glucose in the normal group was 80.5 ± 1.9 $\text{mg}/100$ ml, and 74.0 ± 0.9 $\text{mg}/100$ ml for obese group A ($P < 0.005$) and 72.9 ± 0.8 $\text{mg}/100$ ml for obese group B ($P < 0.001$). These differences were significant between normal subjects and group A ($P < 0.005$) and normal subjects and group B ($P < 0.001$) but not between obese groups.

During the glucose tolerance test all of the glucose values were within normal limits (Fig. 2). The only significantly different value between normal subjects and obese group A was at 240 min ($P < 0.05$). There were no differences between normal subjects and obese group B or between both obese groups.

During the protein-glucose meal (Fig. 3) the normal group had values for glucose significantly higher than obese group A at 180 and 300 min ($P < 0.05$ and 0.01) and than obese group B at 300 min ($P < 0.025$). However, no significant differences were observed between both obese groups.

During arginine stimulation (Fig. 4) the levels of glucose in the normal group were significantly greater than in obese group A at 30, 60, and 90 min ($P < 0.05$, < 0.05 , and < 0.05) and than in obese group B only at 90 min ($P < 0.05$). The values in both obese groups were not significantly different.

Plasma Free Fatty Acids (FFA)

The normal mean fasting level of FFA was 0.621 ± 0.010 $\mu\text{mole}/\text{ml}$ as compared with 0.873 ± 0.056 seen in obese group A ($P < 0.001$) and 0.835 ± 0.030 $\mu\text{mole}/\text{ml}$ in obese group B ($P < 0.001$). There was no significant difference between both obese groups.

During the oral glucose and arginine tests no significant differences in the absolute values in FFA were observed between each of the groups (Figs. 2 and 4). During the protein-glucose meal, however (Fig. 3), obese group B had significantly higher values for FFA than the normal group at 60 and 300 min ($P < 0.025$ and < 0.01) and than the obese group A at 300 min ($P < 0.005$).

When the values for FFA were expressed as mean decrements from the basal level, during the oral glucose tolerance test, there were no significant differences

between the normal group and obese *group A*. At 30 min, however, the normal group achieved a significantly greater decrement than did obese *group B* ($P < 0.05$). Obese *group A* also had a significantly greater decrement than obese *group B* at 30 and 60 min ($P < 0.01$ and < 0.01). No significant differences were observed during either the protein-glucose meal or the arginine tolerance test.

Muscle Protein/DNA and Peak IRI Levels

In previous work [10] the finding of a reduced protein/DNA ratio was made in the muscle of these obese subjects. Figure 5 depicts the relation between these values and the peak insulin response induced by the glucose-protein meal. In the figure the expected protein/DNA ratio (cell size or cytoplasmic index) and the expected peak insulin level for normal children are shown. The figure illustrates the probability that high levels of insulin are required to achieve protein accretion relative to DNA within the muscle.

Discussion

Overweight children were divided initially into two groups depending on duration of obesity. The age of onset differed in that patients in *group A* became obese at 5–8 years of age and the duration ranged from 2 to 4.5 years at the time of study, whereas patients in *group B* were obese from infancy or early childhood and the duration ranged from 6.5 to 15 years. *A priori*, one could consider that the two groups represent different populations. There was an overlap in excess fatness expressed as a percentage of body weight, however, so that the two groups may differ only in age of onset and duration of obesity. Excess fatness must, under these circumstances, increase with age and duration of obesity, and the differences in hormonal response would correlate with either of the situations.

The fasting levels of insulin were abnormally high in patients of *group B*; on stimulation, HGH levels were lower and levels of FFA and insulin were higher. The fact that absolute values for excess fat correlated with circulating amounts of insulin could mean that with increasing "excess fatness" for age or body length the stimulation to the pancreas for insulin release is augmented. If such is the case then the patients under study may represent a single group at different stages.

Paulsen, Richenderfer, and Ginsberg-Fellner [33] demonstrated hyperinsulinemia in obese children and found that those patients with abnormal glucose tolerance had the highest insulin levels. Patients with a family history of diabetes had, on stimulation with

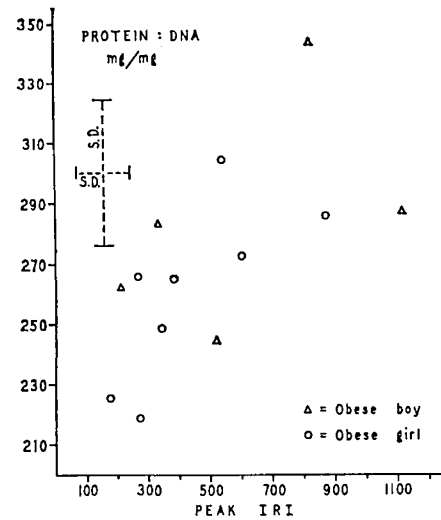


Fig. 5. The muscle cell size (protein/DNA) for obese boys and girls (see reference 10 for data) is plotted against the peak insulin response produced by a protein-glucose meal. On the left side of the figure is shown the cell size for normal children with the standard deviation (300 ± 27 mg protein/mg DNA) and also the expected peak insulin response (161 ± 84 μ U/ml plasma).

glucose, higher insulin levels than those without such a history. Chiumello *et al.* [11] found no differences in insulin levels in obese children with or without a family history of diabetes. They found that once body weight exceeded ideal weight by 35% then hyperinsulinemia existed.

In recent years it has become apparent that in obesity certain tissues become resistant to insulin [20, 29, 36, 40]. Subjects in the present study produced greater than normal amounts of insulin to maintain normal glucose tolerance. *In vitro* studies [20] have demonstrated the relative insulin resistance of intact adipose tissue compared with isolated fat cells in translocating glucose. The question of diffusion of insulin within the connective tissue framework may be important.

With respect to muscle, Stauffacher *et al.* [40] showed that incorporation of 14 C-glucose is significantly reduced in the diaphragm of obese mice. Felig, Marliss, and Cahill [16] have interpreted the rise in levels of valine, leucine, isoleucine, tyrosine, and phenylalanine in the blood of obese patients in the postabsorptive state as indicating tissue resistance to insulin since there is good evidence that increases in plasma insulin inhibits the release of amino acids from muscle [34].

Our own work has shown that the protein/DNA ratio in muscle is reduced in obesity when the base line is organ size or muscle mass. Although some patients have an increase in muscle mass (and muscle

protein content) the increment in the DNA content is even greater. Elsewhere [8] the theory has been postulated that muscle increments in protein relative to DNA reflect the balance between HGH and insulin. If insulin is less effective, then the action of HGH predominates; hence an increase in nuclei number within the musculature is to be expected [10]. Possibly the low circulating levels of HGH seen in this study indicate an excessive uptake by muscle while the reduction of protein relative to DNA indicates the ineffectiveness of insulin. In a sense, then, the reduction of protein/DNA resembles protein deprivation [9] and it is of interest that valine, leucine, and isoleucine also are increased in the circulation in starvation [17].

The prediction that HGH predominates also was suggested by the recent report of Hansen [22] which showed that in uncontrolled juvenile diabetes the imposition of exercise causes a large increase in HGH production. His patients, however, were not obese.

Grodsky [21] studied obese patients after weight reduction and found that pancreatic stimulation no longer produced excessively high insulin levels while Boshell *et al.* [4] did not consider this finding consistent. The weight of evidence would suggest that insulin secretion and excess fatness increase commensurately during the progress of obesity in the human and in the experimental animal [29].

Overnutrition in infancy which has been shown to produce overgrowth [18] may play an extremely important role in determining changes in number and size of cells in different tissues [26, 43]. Such changes may be irreversible if they persist into adolescence or early life [6, 25].

Summary

Studies of levels of plasma insulin, growth hormone (HGH), free fatty acids (FFA), and glucose were performed on 17 obese, nondiabetic children. Children with longstanding obesity had fasting hyperinsulinemia and following stimulation had elevated concentrations of FFA and insulin. All obese subjects had depression of HGH levels. The subjects were divided into two groups depending on duration of obesity. Patients with obesity of short duration (who developed obesity late or at 5–9 years of age) had normal fasting levels of insulin and normal insulin responses to intravenous arginine administration.

Information is presented which suggests a role for insulin in the perpetuation of the obese state and attention is drawn to hyperinsulinemia coincidental

with reduced protein/DNA in muscle. The amount of excess fat correlated closely with a rough estimate of circulating insulin (concentration times volume of distribution).

References and Notes

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