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Diet
fatty acids
insulin

obesity
plasma glucose

Effects of Diet and Weight Loss on Plasma Glucose, Insulin, and Free Fatty Acids in Obese Children

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Summary

In order to determine the relations between insulin and weight changes after diet, oral glucose tolerance tests (OGTT) were carried out before and after diet in 37 obese children aged from 6–16 years, whose weights corrected for height exceeded by at least 2 SD the weights of normal children of the same age and sex.

Five children had not followed the diet and increased during the period of observation both their initial weight excess (from +4.8 to +5.5 SD) and their hyperinsulinemia (total insulin of the OGTT: 359 μU/ml before, 443 μU/ml after).

In 32 children, diet resulted in significant weight loss (from +3.3 to +1.0 SD). Among these, two types of response to diet could be distinguished. 1) In 25 children, the initially elevated insulin responses returned to normal or near normal values (mean sum of all five insulin values 282 μU/ml before, 144 μU/ml after diet), insulin and weight changes being positively correlated. The younger children had better results than the older ones. 2) Seven children, although also having lost weight, showed an increase of insulin responses from initially normal to secondarily elevated values (mean total insulin 133 μU/ml before, 260 μU/ml after diet).

Age of onset, duration of obesity, and duration of diet were not related to either weight or insulin changes. The results indicate that in the majority of cases hyperinsulinism observed in childhood obesity is reversible by diet in correlation with weight loss.

Speculation

Dietetic factors seem to play an important role in inducing reduction of hyperinsulinism and weight loss in obese children, yet they are not the only ones. Several not only physiologic but also psychologic and environmental factors are involved in the treatment of obesity and might be responsible for the paradoxical evolution of some subjects whose insulin responses were not decreased but increased during diet. Further follow-up and new investigation of these patients will be necessary to reveal whether they constitute a group of different etiology and prognosis in terms of obesity.

Hyperinsulinism in obesity is well documented; however, its casual role in the development of obesity is still poorly understood in children. The elevation of plasma insulin is probably due to β cell overproduction (11), yet the origin of this hypersecretion continues to be discussed. Is it the cause or the consequence of obesity, or are both hyperinsulinism and obesity the consequence of an intestinal or dietary disorder? In a previous study (6) analyzing the OGTT results of 158 obese children, we found that insulin responses were already increased in very young children at the beginning of obesity, and that further elevation was influenced by increasing age rather than by longer duration of obesity.

In experimental overnutrition, rapid elevation of insulin levels has been demonstrated (15, 22); on the other hand, the improvement of obese hyperinsulinism after diet with or without weight loss has been reported (3, 9, 10, 18), suggesting that nutritional factors may play an important role.

In the study of obesity and hyperinsulinism, children are privileged subjects, since obesity is of relatively recent onset and secondary disorders due to long term obesity are limited. However, there is poor information on the effects of diet in obese children (5). The present study was undertaken in view to analyze, in a sample of obese children, glucose, insulin, and free fatty acid changes in relation to weight loss after dieting.

PATIENTS AND METHODS

Thirty-seven obese children, 20 boys and 17 girls, aged from 6–16 years, attending the outpatient clinic for obesity, not yet treated, and who were not suffering from any other troubles were investigated after obtaining their own and their parents' informed consent. The definition of obesity was based, in agreement with the principles of Fomon (8), on standard curves of weight and height according to age and sex established for French children by Sempé and Pedron (21). The degree of obesity expressed as the difference, in standard deviations (SD), between weight and height for age according to sex, exceeded by at least 2 SD the values of normal children (example: patient C.G., male, age 8.5, weight 34 kg (+4 SD), height 132 cm (+1 SD), degree of obesity (+3 SD)).

Fat cell sizes determined by abdominal wall fat tissue biopsy were increased in all cases (mean diameter 107.0 ± 4.24 μm). The subscapular skinfold thickness values correlated well with both weight excess and fat cell size (16).

After a standard OGTT using 30 g glucose/m^2 body surface, the obese children were put on a moderately restrictive diet containing 1200–1500 cal/day according to age, and consisting of 45–50% carbohydrate, 30–35% lipids, and 15–20% protein. In addition, they received instructions for dividing total food into four equal meals.

A second OGTT was performed after a period ranging from 3–24 months, during which 32 patients had obtained satisfactory weight loss and the increased fat cells had returned to normal size, and 5 patients had refused or given up the diet and had gained weight. The patients were advised to eat normal amounts of carbohydrate for 3 days before the second test.

During the tests, plasma glucose was measured by the glucose oxidase method, immunoreactive insulin (IRI) by the radioimmunoassay of Yalow and Berson (25) with separation by charcoal, and free fatty acids (FFA) by the technique of Duncombe (7).

For analysis of glucose and insulin data we used both, the values of each sampling time, and the sum of all five test values as an appreciation of the total response (ΣG and ΣIRI, respectively). The insulinogenic index was expressed as the sum IRI/sum G ratio.

The results were analyzed for two age groups separately: group A, 6–10 years, group B, 11–16 years. Indeed, previous studies have shown significant differences of insulin levels of obese children at different ages (6). Seventy healthy children studied in this laboratory under identical conditions (12) served as controls.

RESULTS

The main clinical data relative to age, sex, age of onset, and duration and degree of obesity before and after diet are presented in Table 1. After dieting, 32 children had lost variable amounts of weight which were not related to the duration of the treatment. The mean initial weight excess of +3.3 SD fell to +1.0 SD. Now 29 children were within normal limits, *i.e.*, below +2.0 SD. Three children still were obese, showing a degree of obesity of +2.2, 2.5, and 2.7 SD, respectively. Their weight loss was important, however, since before treatment their weight excess had been particularly severe: respectively, +3.8, 5.2, and 5.6 SD. In contrast, 5 children who had not dieted had increased their degree of obesity.

The younger children of group A, although slightly more obese before treatment, lost more weight and reached a better final result than the older ones (Table 2); however, these differences are not significant.

The results of the OGTTs performed before and after weight loss are presented in Table 2 and Figures 1 and 2. The results of the first test are comparable to those obtained previously in 158 obese children (6); the elevation of insulin levels and the differences between age groups are identical.

After diet, important changes, particularly in insulin values, were present. In group A (Fig. 1), blood glucose, normal before diet, remained unchanged. The mean insulin response, however, decreased significantly at 30, 60, and 180 min, returning completely to that of normal weight children of the same age, and even below, at 30 min. The total insulin response also diminished significantly. The insulinogenic index, which had been increased before diet, decreased to normal. The FFA curve decreased as a whole, but these changes were not significant.

In group B (Fig. 2), mean blood glucose, although within normal limits before treatment, decreased significantly at 30 and 120 min and even fell below the normal means. The diminution of the mean insulin response, significant at 30 min only, was yet important on the whole (significant decrease of total insulin, Table 2). At 120 min, there remained a slightly significant elevation ($P < 0.05$) compared to normal. The sum insulin/sum glucose ratio hardly decreased and remained above normal. The mean FFA level, within normal limits at the first test, fell significantly at 0 and 30 min.

The five children who had put on weight during the same period exhibited opposite changes in OGTT results. Glucose as well as insulin values increased (Table 3), and so did fasting FFA values: 726 μEq/liter for the first test, 904 μEq/liter for the second one.

Although, on the average, the most marked effect on OGTT in dieting and weight-losing children was the diminution of hyperinsulinemia, this was not present in all cases. When examining individual tests, we noticed seven children who had normal insulin responses before dieting and increased responses after. All seven had lost weight by dieting, but significantly less ($P < 0.05$) than the children whose insulin responses had been elevated before and decreased after dieting (Table 3); in spite of an initially less severe obesity, they reached a less satisfactory final weight index.

Table 3 presents the main difference between the three groups of obese children, according to the type of response to treatment by diet: 1) no diet (five subjects), weight gain and aggravation of hyperinsulinism; 2) 25 "good responders," weight loss and reduction of hyperinsulinism; 3) 7 "paradoxal responders," weight loss and increase of insulin values. Age, sex, age of onset and duration of obesity, as well as duration of diet, were comparable in all groups.

Analysis of correlations was made between different factors implied in the development of obesity, such as hyperinsulinemia and weight excess before and after diet, as well as insulin and weight changes after diet. Age, sex, age of onset, and duration of obesity were not found to be related to any of these variables.

A positive linear relationship was found between reduction of plasma insulin (difference between sums of both tests) and 1) the degree of hyperinsulinemia (insulin sum) before diet ($r = 0.74$, $P < 0.01$); 2) the degree of obesity before diet ($r = 0.53$, $P < 0.01$); 3) weight loss after diet ($r = 0.63$, $P < 0.01$). In addition, weight loss was positively correlated with 1) the degree of hyperinsulinemia before diet ($r = 0.43$, $P < 0.02$); 2) the degree of obesity before diet ($r = 0.76$, $P < 0.01$); which itself was related to the

Table 1. *Clinical data of obese children*[1]

Group	*n*	Sex	Age (years)	Age of onset of obesity (years)	Duration (years)	Degree of obesity (SD) Before	Degree of obesity (SD) After diet	Difference (SD)	Duration of diet (mo)
I	5	2 M	11.5	4	7	4.8	5.5	0.7	13
		3 F	(6–14)	(>1–7)	(2–12)	(2.3 to 7.5)	(2.4 to 8.5)	(0.1 to 1.8)	(7–18) No controlled diet
II	32	18 M	11.1	4.9	6.2	3.3	1.0	−2.3	8
		14 F	(6–16)	(>1–13)	(1–12)	(2.0 to 5.6)	(−0.4 to 2.7)	(−0.8 to −5.5)	(3–24)

[1] Means and ranges (in parentheses) Group I: 5 children who had gained weight; group II: 32 children who had lost weight.

Table 2. *Mean ± SEM of total insulin responses and total insulin/total glucose ratios during OGTT, and of weight index before and after weight loss in obese children, according to age*[1]

Group	*n*	Age (years) and range	ΣIRI (μU/ml) Before	ΣIRI (μU/ml) After	Difference	ΣIRI/ΣG Before	ΣIRI/ΣG After	Degree of obesity (SD) Before	Degree of obesity (SD) After	Difference
A	13	8.4	165	100[1]	−65	34	20[1]	+3.3	+0.9[1]	−2.4
		(6–10)	±21.9	±14.0		±3.7 (×10⁻²)	±2.4 (×10⁻²)	±0.25	±0.20	±0.23
B	19	12.4	304	209[1]	−95	59	46	+3.1	+1.2[1]	−1.9
		(11–16)	±43.1	±22.2		±7.9 (×10⁻²)	±5.2 (×10⁻²)	±0.24	±0.19	±0.21

[1] Significant differences between before and after diet values.

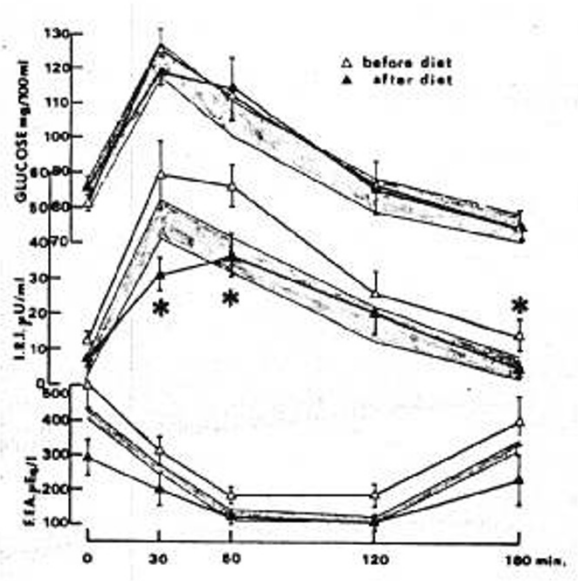

Fig. 1. Mean OGTT results ± SEM of 13 obese children aged from 6–10 years (group A), before and after diet. Shaded area: means ± SEM of 21 normal children of the same age. (*) Significant differences between before and after diet values.

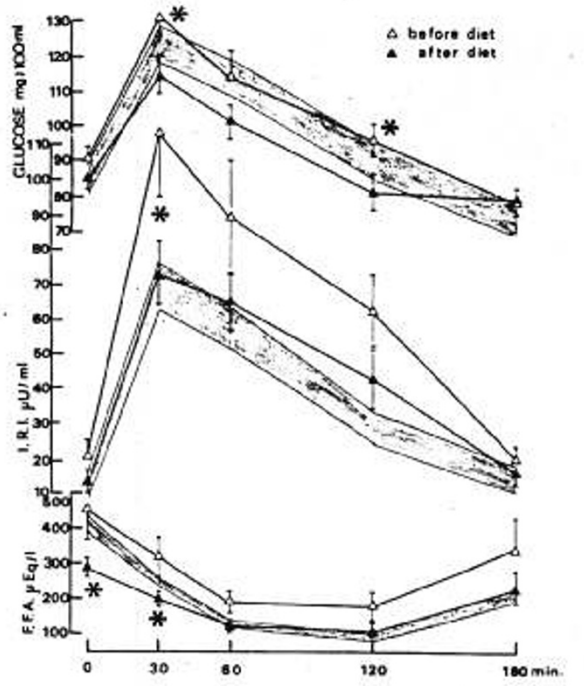

Fig. 2. Mean OGTT results ± SEM of 19 obese children aged from 11–16 years (group B), before and after diet. Shaded area: means ± SEM of 33 normal children of the same age. (*) Significant differences between before and after diet values.

insulinemia before diet ($r = 0.38$, $P < 0.05$) and to the degree of obesity after diet ($r = 0.41$, $P < 0.02$).

DISCUSSION

The results confirm the total or partial reversibility by diet and/or weight loss of some of the metabolic and hormonal disorders characteristic of the obese, such as diminished glucose tolerance and hyperinsulinism, reported by several investigators (1, 3, 9, 10, 20). The interpretation of this proposed by each author depends on his conception of the origin of these disorders in the obese, which still remains speculative. In any case, the finding of the reversibility of hyperinsulinism by or concomitant with weight loss does not support the hypothesis of primary hyperinsulinism being a common cause of obesity.

Salans *et al.* (20) believe that hyperinsulinism is an adaptative process in order to compensate the loss by adipose tissue of its sensitivity to insulin due to their big cell size, and that weight loss, by reducing fat cell size and thereby insulin resistance, restores normal insulin secretion.

Archer *et al.* (1) demonstrated a lack of receptors on the lymphocytes of obese subjects who fixed significantly less insulin than those of normal subjects. The capacity of fixation was improved by a short period of caloric restriction followed by weight loss, without changes of the insulin response.

Brook and Lloyd (3) studied two groups of obese children, both treated by low calorie, poor carbohydrate diet. The first group, still attending to the diet, showed significantly reduced insulin levels, while the other, who had previously returned to nearly normal food intake, exhibited insulin values as high as before treatment. However, weight loss and reduction of fat cell size were comparable in both groups. This finding suggests the responsibility of food composition and food absorption in the development of hyperinsulinism as well as its regression.

Among the 32 children of the present study who obtained significant weight loss after dieting, 25 children showed concomitant return of their initial hyperinsulinemia to normal or near normal values. The younger children obtained better results compared to the older ones. The diminution of the total insulin response was related to the degree of initial hyperinsulinemia, to the degree of obesity before, and to the weight loss after diet.

Seven children, however, showed a paradoxal evolution: their insulin responses, which at the first test had been within the normal ranges, were found to be significantly elevated at the second one; they lost weight by dieting, but significantly less than the former group. Since it had not been possible to obtain the repetition of the OGTTs, only a single test was available in each case. Some criticism might arise from the lack of reliability of the OGTT because of accidental variations, difficult to appreciate. We believe, however, that the differences observed between the two groups exceed largely that type of variation and that their significance may be admitted.

But what is the explanation of this observation? One reason could be the disobedience by these patients of the dietary prescriptions, although no admission was made of this. Indeed, we had no control other than the questioning over what happened in the families; thus we do not really know whether our recommendations were followed effectively. The intake of an excessive amount of carbohydrate without notable increase of total calories might have caused the observed rise of insulin secretion without affecting

Table 3. *Mean OGTT and weight changes in obese children, according to their response to dietary prescriptions*[1]

		ΣIRI(μU/ml)			ΣG(mg/100 ml)			Degree of obesity (SD)			
Group	*n*	Before	After	Difference	Before	After	Difference	Before	After	Difference	Diet
I	5	359	443	+84	451	544	+93	+4.8	+5.5	+0.7	–
II	25	282	144	−138	510	464	−46	+3.4	+0.9	−2.5	+
III	7	133	260	+127	465	475	+10	+2.9	+1.5	−1.4	+?

[1] Group I: no diet (IRI ↑, weight ↑), group II: good responders (IRI ↓, weight ↓), group III: paradoxal responders (IRI ↑, weight ↓).

weight loss, thus reproducing to a certain extent the experimental conditions of the second group described by Brook (3).

In recent years, a growing number of investigators have emphasized the role of dietary factors not only in the constitution of obesity, but also in the development of hyperinsulinism.

Machinot *et al.* (13) compared the spontaneous food intake of obese children to that of normal weight children and found striking differences as well in quantity (all obese eat more), as in quality (preference of carbohydrate-rich food) and in feeding rhythm (shifting towards the evening hours).

On the other hand, several experiments reproducing the obese eating habits were followed by hormonal and metabolic disorders, with or without accumulation of fat. In rats, periodic hyperphagia compared to nibbling resulted in multiple anomalies in adipose tissue and intermediate metabolism (4, 24).

In experimental obesity due to overnutrition for 3–5 months in man, Sims and Horton (22) found metabolic and hormonal changes identical to those of spontaneous obesity and, in addition, the development of an obesity-like feeding rhythm in some subjects.

After only 1 week of experimental overnutrition, Olefsky *et al.* (15) obtained modifications of blood glucose, insulin, and lipids in normal subjects, without significant weight gain.

Similar modifications have been obtained by changing the food composition. In normal (17) and obese subjects (9), rich carbohydrate diets were followed by significant elevations of plasma insulin compared to isocaloric, poor carbohydrate diets, without affecting weight. Rodger *et al.* (18) observed increased insulin levels when they changed the type of dietary carbohydrate from polysaccharides to simple sugars.

In the obese, the β cell-stimulating action of glucose is much more efficient when administered orally than intravenously (14, 23). Probably the enteral factor, which is likely to be the gastric inhibitory polypeptide (5) until its exact definition, is responsible for this difference. The exaggerated insulin response seen in the obese might be due to a greater gastric inhibitory polypeptide-mediated insulin release induced by an excessive carbohydrate ingestion, which at the same time by caloric overconsumption leads to weight gain.

Following this hypothesis, successful treatment should take into account two distinct actions: caloric restriction will result more particularly in the loss of body fat, whereas carbohydrate restriction will be necessary to improve hyperinsulinemia. Another factor is the regular distribution of meals, to which we accorded great attention in our patients, since we believe it to be essential to the success of diet. Yet the role played by the feeding rhythm in obesity is not well elucidated at present.

Whether weight loss and regression of hyperinsulinism are only paralleling or also influencing each other, remains to be determined. Most investigators did not find any correlation between the two factors. In the present study, however, consistent with the majority of our cases and in spite of some exceptions, they were significantly related, but this relationship is not necessarily a causal one. Jackson *et al.* (10), on the other hand, having examined obese subjects several months after a period of total fasting, found a correlation between insulin changes during fasting and the weight changes following that period; in other words, the capacity to maintain or to continue weight loss after fasting was related to the previous reduction of hyperinsulinism.

This finding suggests that the reduction of hyperinsulinism is not only a subordinate effect of weight loss, but plays by itself an essential role in overcoming obesity. This is important especially for long term prognosis, which in fact is very bad. Fifty to 80% of obese children are still obese when adult (2, 18). Certainly the reasons of failure of treatment are complex, implying not only physiologic, but also psychologic and environmental problems. We believe, however, that the normalization by treatment of the hormonal and metabolic disorders constitutes a favorable prognostic sign, and that failure to improve them might prevent continuation or maintenance of weight loss. Further follow-up and new investigation of our patients will be necessary to consolidate this hypothesis. These might reveal, too, whether some fortuitous factor was responsible of the paradoxal evolution of those patients whose insulin responses were not decreased but increased by diet and weight loss, or whether inside obesity they constitute a group of different etiology and prognosis.

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