Relationship between Obesity, Chemical Diabetes and Beta Pancreatic Function in Children

Giuseppe Chiumello, M.D., Maria Jose Del Guercio, M.D., Margherita Carnelutti, M.D., and Giovanni Bidone, M.D., Milan, Italy

SUMMARY

Seventy-nine children, aged two and one-half to thirteen years, divided into four groups on the basis of their weight and family history of diabetes mellitus (one sibling or one parent with insulin dependent diabetes), were examined. The data showed that the occurrence of chemical diabetes was higher in children with family history of diabetes. In obese children hyperinsulinism was present, but glucose intolerance was associated with impairment of insulin secretion. The findings suggest that there probably is a genetically predisposed incapacity of beta cells to respond to various stimuli, and diabetes may develop in the face of relative insulin deficiency, regardless of the absolute value of plasma insulin. DIABETES *18*:238-43, April, 1969.

Obesity in adults has been associated with a marked increase in frequency of abnormalities of carbohydrate metabolism by a number of investigators.[1,2] Diabetic glucose tolerance responses have been reported to reach a prevalence of 60 to 70 per cent in some obese populations.[2,3]

The problems of obesity in childhood have been less extensively evaluated. Although some authors have reported cases of decreased glucose tolerance in obese children,[4,5] and recently Paulsen reported a prevalence of abnormalities in 23 per cent of the subjects examined[6] the frequency is lower than the percentage in adult age.

In a systematic study of obese children, we were impressed by the relatively low frequency of impaired glucose tolerance in the obese child.[7] The purpose of the present study is to delineate the factors that may explain these observed differences in childhood and adult obese populations. We considered the interrelationship between obesity, glucose tolerance, beta pancreatic function and the role of a strong family history of diabetes.

MATERIAL AND METHODS

Patient population.

Seventy-nine children, aged two and one-half to thirteen years, were divided into four groups on the basis of their weight and family history of diabetes. Subjects with one sibling or parent with insulin dependent diabetes were classified as having a strong family history of diabetes. No subject had clinical symptoms of diabetes.

Group I. Twenty-one children (twelve males and nine females) of normal weight *without* family history of diabetes whose mean age was 8.7 yrs. (range 6 to 11 yrs.).

Group II. Twenty children (ten males and ten females) of normal weight *with* strong family history of diabetes whose mean age was 8.4 yrs. (range 5 to 11 yrs.)

Group III. Twenty-two obese children (thirteen males and nine females) *without* family history of diabetes whose mean age was 9 yrs. (range 2½ to 13 yrs.) and mean weight was 66.19 per cent greater than ideal weight* (range 41.66 to 117.39 per cent).

Group IV. Sixteen obese children (seven males and nine females) *with* strong family history of diabetes whose mean age was 8.3 yrs. (range 4 to 11 yrs.), and whose mean weight was 78.29 per cent greater than ideal weight (range 35.71 to 105.71 per cent).

Group I subjects were children of normal weight admitted to the hospital for mild respiratory disease and submitted to test just prior to discharge.

The duration of the obesity (groups III and IV) varied from 1 to 4 yrs. None of the subjects had lost

From the Department of Pediatrics and Child Health, University of Milano, Via Commenda 9, Milano 20122, Italy.

*Ideal body weight was calculated from the tables of Stuart and Meredith[8] and expressed as function of height.

weight for a period of several months preceding the observations.

The oral glucose tolerance test was performed after three days of normocaloric diet, with 50 per cent of total calories as carbohydrates. After an overnight fast, 2 gm./kg. of body weight of glucose in 200-300 ml. of flavored water were given in five minutes. The dosage of glucose was determined from the actual weight in children of normal weight, and from the ideal weight, in obese children. Zero time was taken to be at the beginning of the drink and samples were drawn at 30, 60, 90, 120 and 150 minutes for the determination of blood sugar and plasma insulin. Capillary blood sugar was determined by the method of Somogyi-Nelson[9]; insulin was determined by the double antibody technic[10] in plasma obtained from the antecubital vein. In our laboratory, the mean coefficient of variation on samples, for the radioimmunoassay of insulin, was 5 per cent.

Chemical diabetes was defined as the presence of an abnormal oral glucose tolerance, according to the criteria of The British Diabetic Association[11] and Committee on Professional Education, the American Diabetes Association.[12] These criteria were based on adult population studies but could be applied to children as shown by the studies of Burkeholder et al.[13] of oral glucose tolerance test in normal children.

In all subjects found to have chemical diabetes, the glucose tolerance was repeated at least twice under the controlled conditions stated previously. The variations of insulin levels were usually less than 15 per cent from the mean when the test was repeated in the same subject.

The mean area subtended by plasma insulin concentration curves was determined in the four groups of subjects.[14] The insulin response was expressed also as increment per cent above the basal insulin level.

RESULTS

Of the seventy-nine children studied, twelve were found to have an abnormal glucose tolerance test. In further analysis of the data, subjects with normal glucose tolerance (table 1) and subjects with abnormal glucose tolerance (table 2) were considered separately. Figure 1 and table 1 demonstrate the plasma insulin responses after glucose loading in nonobese and obese subjects with normal glucose tolerance. In the obese, although they had normal blood sugar levels, high fasting insulin levels were found, and higher and more sustained insulin response was observed. No significant difference could be found in insulin response when the presence or absence of a family history of diabetes was considered.

The data of children with abnormal glucose tolerance are shown in table 2. There were twelve subjects, six of normal weight and six obese. Eleven had a strong

TABLE 1

Blood sugar and plasma insulin levels* in subjects with normal oral glucose tolerance test

Minutes:		0	30	60	90	120	150
Group I (21) (Normal weight)	Blood sugar (mg. per 100 ml.)	75.9 ±15.2	126.9 ±26.2	114.0 ±25.3	103.4 ±13.5	97.2 ±12.7	91.4 ±14.7
	I.R.I. (μU./ml.)	15.2 ± 5.3	79.2 ±24.2	64.8 ±18.8	44.4 ±15.2	31.8 ±10.5	22.8 ±10.3
Group II (14) (Normal weight with family history of diabetes	Blood sugar (mg. per 100 ml.)	72.6 ± 3.7	125.7 ± 6.5	113.7 ± 7.1	100.2 ± 7.0	92.1 ± 6.0	80.8 ± 6.5
	I.R.I. (μU./ml.)	13.3 ± 2.0	71.9 ± 9.6	62.1 ± 6.6	46.7 ± 5.0	34.0 ± 4.7	24.9 ± 4.0
Group III (21) (Obese)	Blood sugar (mg. per 100 ml.)	75.5 ± 3.6	133.0 ±10.1	119.5 ± 9.0	101.8 ± 7.8	91.2 ± 5.5	82.4 ± 5.1
	I.R.I. (μU./ml.)	51.5 ± 6.1†	224.2 ±37.5†	267.1 ±49.3†	202.1 ±57.8†	157.0 ±16.5†	128.9 ±11.0†
Group IV (11) (Obese with family history of diabetes)	Blood sugar (mg. per 100 ml.)	74.1 ± 3.7	133.4 ±11.4	116.3 ± 9.0	100.5 ± 7.1	89.7 ± 5.3	78.1 ± 4.1
	I.R.I. (μU./ml.)	47.3 ± 8.0†	198.2 ±49.9†	260.4 ±42.4†	201.2 ±33.9†	162.9 ±32.6†	112.8 ±18.5†

*Mean ± S.E.M.
†$p < 0.01$: significance of the difference between normal weight and obese children.

TABLE 2

Blood sugar and plasma insulin levels* in subjects with abnormal oral glucose tolerance test

Minutes:		0	30	60	90	120	150
Normal weight(6)	Blood sugar (mg. per 100 ml.)	82.8 ± 9.6	179.8 ±11.4†	188.0 ±13.1†	167.0 ±10.7†	154.0 ± 8.3†	144.0 ± 8.8†
	I.R.I. (μU./ml.)	14.4 ± 1.6	36.0 ± 9.1†	41.2 ± 9.2†	49.0 ±13.1	38.0 ± 9.6	26.6 ± 8.2
Obese (6)	Blood sugar (mg. per 100 ml.)	84.6 ±10.0	175.4 ±13.1†	189.0 ±17.2†	181.9 ± 5.1†	170.0 ± 8.9†	157.0 ±16.1†
	I.R.I. (μU./ml.)	43.6 ±14.8	114.0 ± 3.0†	134.4 ±16.6†	136.8 ±17.1†	138.8 ±57.3	117.6 ±25.2

*Mean ± S.E.M.
†$p < 0.01$: significance of the difference between subjects with normal glucose tolerance test and subjects with chemical diabetes

family history of diabetes (six normal weight and five obese). Figure 2 illustrates that fasting insulin levels were similar to those of the appropriate weight control group, but the insulin response was decreased.

The absolute values of insulin in obese children with chemical diabetes were found to be greater than those of normal weight subjects with normal glucose tolerance. Comparison of insulin response in obese children with chemical diabetes mellitus (figure 2) and obese children with normal oral glucose tolerance test (figure 1) showed the former to have decreased insulin response. In figure 3 the total insulin secretion was arbitrarily expressed as the mean area of subtended insulin curves during the test. Comparison by this method demonstrated that the diabetic state was associated with decreased insulin secretion whether the subjects were of normal weight or obese.

In figure 4 the insulin response was expressed as increment per cent above the basal value. Subjects with normal and abnormal glucose tolerance could be differentiated into two groups on the basis of their insulin response by this method. This differentiation was applicable to both normal weight and obese subjects. In basal conditions and after stimulation no correlation was found between excess weight and plasma insulin, either in absolute value or increment per cent above fasting level. The hyperinsulinism in our cases was observed when the weight of our patients was more than 35 per cent over their ideal weight, but no constant relationship was found between the total or excess of body weight or total fat mass* (see footnote page 241) and the degree of hyperinsulinism.

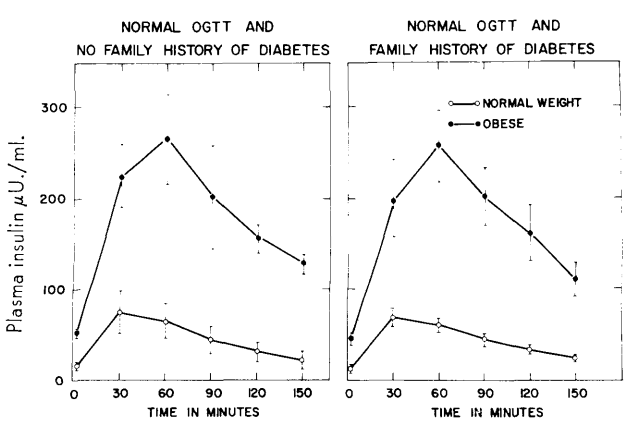

FIG. 1. Plasma insulin levels (mean ± S.E.M.) after oral glucose load in normal weight and obese children with and without family history of diabetes, with normal glucose tolerance.

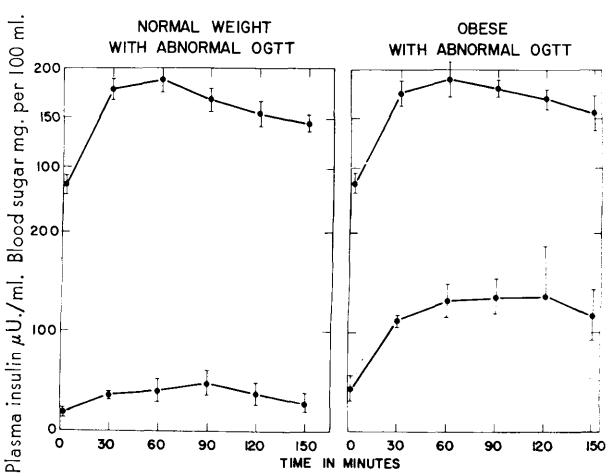

FIG. 2. Blood sugar and plasma insulin levels (mean ± S.E.M.) after oral glucose load in normal weight and obese children with decreased glucose tolerance.

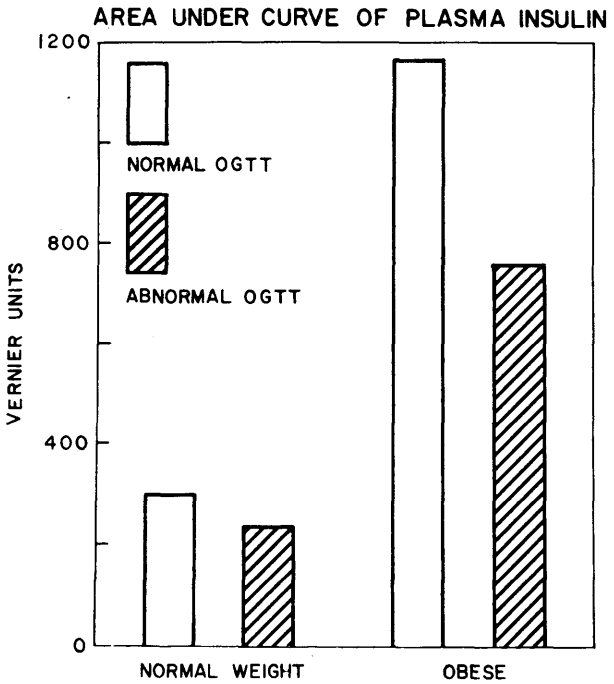

FIG. 3. Area (mean ± S.E.M.) subtended by plasma insulin curves during oral glucose tolerance test in normal weight and obese children with normal and decreased glucose tolerance.

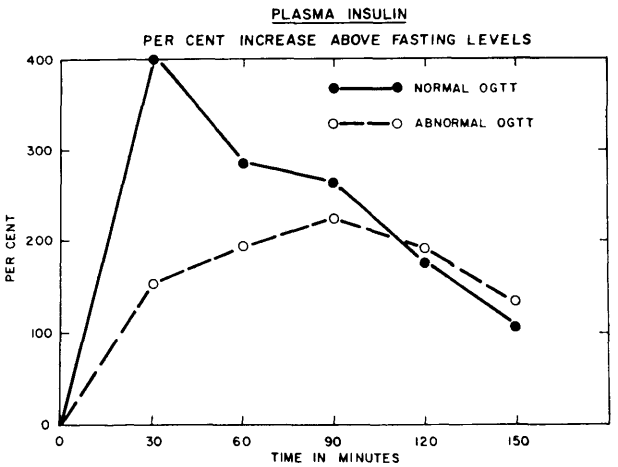

FIG. 4. Plasma insulin as per cent increase above fasting level during oral glucose tolerance test in children with normal and decreased glucose tolerance.

DISCUSSION

In obese children with a normal glucose tolerance, the fasting plasma insulin values and the response to glucose were higher than in nonobese children. Similar observations have been reported in the adult in recent years[16,17] and confirmed to be a constant feature also in obese children.[6,18]

The factors involved in this abnormal response are not known. This "insulin resistance" has not been shown to be dependent on adrenal hyperfunction[19] or hypersecretion of GH[20,21] or on high levels of FFA.[22] Changes in glucose metabolism and insulin responsiveness correlate with the tissue FFA pool rise[22] and the intracellular deficiency of potassium.[23] The possible influence of these findings in obesity has not yet been clearly evaluated, however.

Recent in vitro studies of isolated adipose tissue have demonstrated that insulin activity, measured as an effect on oxidation rate of glucose is related to the size of the adipose cell.[24] The large cell of obese subjects has a decreased responsiveness, but loss of weight and reduction in adipose cell size bring a normalization of their activity. These findings in vitro equate well with the plasma hyperinsulinism and suggest that reversible peripheral tissue factors play an important role in the insulin-glucose abnormality in obesity.

Another explanation for the elevation of plasma immunoreactive insulin could derive from insulin precursors. The recent report of proinsulin by Steiner's group[25] and the possibility that the big insulin reported by Roth[26] with decreased biological activity, but measured as insulin in the radioimmunoassay, can be the same material, are promising leads in the investigations of hyperinsulinism.

The relationship of obesity, maturity onset diabetes and beta pancreatic function in adults so far is not completely clear. Two main hypotheses are currently advanced. First, some investigators have stated[16,20] that insulin resistance is the primary cause of an abnormal glucose tolerance in the obese. These investigators did not find evidence for a decreased insulin reserve in their subjects. Only in the presence of severely impaired glucose tolerance without ketoacidosis was there demonstrated an impaired plasma insulin response, indicating a state of insulin deficiency.

Secondly, other investigators[27] have reported that the rate of insulin release and the quantity of insulin secreted per unit of glycemic stimulus is greater in normal subjects than in mild diabetics regardless of body weight. Karam[28] also demonstrated that the obese maturity onset diabetic and nondiabetic subjects have comparable high serum insulin levels after glucose, whereas the nonobese maturity onset diabetes, despite

*Total fat mass was calculated according to the formula of Cheek.[15]

marked hyperglycemia, does not. Thus, the excess insulin response to glucose noted in maturity onset diabetes correlates with obesity. Evidence supporting a relation of the diabetic state with decreased beta pancreatic function, regardless of body weight, is reported by others.[29,30]

The data presented herein demonstrate a decreased peripheral insulin response after oral glucose in the obese child with abnormal glucose tolerance, whether the beta pancreatic function is expressed as insulin release (μU./ml.) or as increment per cent above fasting levels. The observations that the obese child with chemical diabetes shows a decreased pancreatic response when compared to the obese child with a normal glucose tolerance does not support the first hypothesis,[16,20] although we cannot exclude the possibility of a secondary exhaustion.

In assessing the relationship between family history of diabetes mellitus and beta pancreatic function in children with normal glucose tolerance at the time of the study, we did not find any difference in insulin response in subjects with or without family history of diabetes mellitus. This does not exclude, however, the possibility of decreased beta pancreatic function which could perhaps be demonstrated with greater and more sustained stimuli. Prediabetes (both parents diabetic; homozygous twin of a diabetic) has been reported to be associated with decreased insulin secretion, even in the presence of a normal oral glucose tolerance test.[31] Decreased insulin secretion in prediabetic subjects can also be demonstrated with a cortisone-glucose test[32] or with a rapid[33] or sustained[34] intravenous infusion of glucose.

Paulsen[6] has reported that obese children with near diabetic relatives with normal or moderately abnormal glucose tolerance have higher levels of insulin than normal subjects. Children in the group classified as having markedly abnormal glucose tolerance tests, however, have decreased insulin response. In our study all the normal weight children with chemical diabetes had a strong family history of insulin dependent diabetes. The decreased insulin secretion in this group suggests that in children the disorder is characterized by a decrease of beta pancreatic function both in chemical and clinical diabetes.[35,36]

The absolute values of insulin in obese children with chemical diabetes were found to be greater than those of normal weight subjects with normal glucose tolerance. But comparison of insulin response in obese children with chemical diabetes and obese children with normal oral glucose tolerance revealed the former to have decreased insulin response.

We have attempted to assess the importance of the influence of obesity in the possible evolution of diabetes mellitus. In children with apparently normal genetic background, there is no positive relationship between obesity and the occurrence of chemical diabetes. It should be emphasized that all but one subject with chemical diabetes had a strong family history of diabetes mellitus. Nevertheless, the possibility of obesity as an additional stress factor on children with a genetic predisposition must be considered. Although the limited number of subjects examined does not permit any conclusion of statistical significance, the frequency of chemical diabetes in our series is close to that reported by others in normal weight children with similar genetic background.[37,38]

In conclusion, our data suggest that the prevalence of chemical diabetes is higher in children with a strong family history of diabetes. In obese children, as in adults, hyperinsulinism is present, and the development of glucose intolerance is associated with impairment of insulin secretion. This is probably related to a genetically predisposed incapacity of beta cells to respond to various stimuli. Diabetes develops in the face of relative insulin deficiency, regardless of the absolute value of plasma insulin.

With the limitations of the number of subjects examined, obesity per se cannot be interpreted to represent a state of latent diabetes, but it can be looked on as an additional stress in subjects who carry an inherited tendency to the disease. The high prevalence of diabetes in obese adults can be an indication of the effect of the duration of obesity on the progressive impairment of glucose tolerance.

In obese children, decreased beta pancreatic function was demonstrated when abnormal glucose tolerance was present. The basic defect of juvenile diabetes mellitus was a deficiency of beta cell function, and in these children, the hyperinsulinism associated with obesity did not appear to alter this basic defect.

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