Plasma Insulin and Growth Hormone Levels in Untreated Diabetic Children

C. G. THEODORIDIS, G. W. CHANCE, G. A. BROWN, and J. W. WILLIAMS

From the University of Birmingham, Institute of Child Health, Birmingham

Theodoridis, C. G., Chance, G. W., Brown G. A., and Williams, J. W. (1970), *Archives of Disease in Childhood*, 45, 70. **Plasma insulin and growth hormone levels in untreated diabetic children.** Blood glucose, plasma insulin, and growth hormone were measured in 28 untreated diabetic children, and the results were compared with those obtained from a control group. Though 2 of the 28 diabetic children were still capable of increasing plasma insulin concentration above the normal fasting range, the insulin response was inadequate in all cases. Growth hormone levels in the fasting diabetic children were not raised; however, in the non-fasting children whose illness was of greater severity they were raised despite the presence of hyperglycaemia.

There is little published information on plasma insulin and growth hormone levels in diabetic children at the time of diagnosis. Two recent reports contain conflicting results. Drash *et al.* (1968) found low fasting insulin levels, while Parker *et al.* (1968) reported normal values in newly diagnosed diabetic children. Their growth hormone results were also at variance. Parker *et al.* (1968) found normal growth hormone levels during fasting and after an oral glucose load or arginine infusion, while Drash *et al.* (1968) reported raised fasting plasma growth hormone and levels significantly higher than their control group after the intravenous infusion of arginine.

We wish to report the results of plasma insulin and growth hormone estimations obtained before treatment in 28 diabetic children.

Patients and Methods

Investigations were made on 28 newly diagnosed diabetic children, 14 girls and 14 boys, with an age range of 1 year 8 months to 13 years 5 months. None had been treated with insulin at the time of blood collection; 6 were fasted for 12 to 15 hours before blood collection (Cases 1-6). 22 required urgent treatment (Cases 7-28), and venous blood was taken immediately after admission to hospital for glucose, insulin, and growth hormone measurement.

Control data were obtained from 16 non-obese metabolically normal children, 9 boys and 7 girls, whose ages ranged from 2 years 7 months to 15 years 2 months.

Venous blood was collected from a peripheral vein with minimal stasis. Aliquots were transferred to fluoride-oxalate tubes for glucose analysis and to heparin tubes for insulin and growth hormone assays. Plasma was stored at -20°C . until assayed.

Blood glucose was determined by an automatic glucose-oxidase method described by Discombe (1963). Plasma insulin was measured by a double antibody radioimmunoassay procedure similar to that described by Morgan and Lazarow (1963), and the plasma growth hormone was measured by the double antibody radioimmunoassay method of Hartog *et al.* (1964).

Results

The blood glucose, plasma insulin, and growth hormone results from the control children and from the diabetic children are shown in Tables I and II.

In the control group fasting blood glucose values ranged from 56 mg./100 ml. to 79 mg./100 ml. (mean 64.9 mg./100 ml.). Plasma insulin values ranged from 2 $\mu\text{U}/\text{ml}$. to 21 $\mu\text{U}/\text{ml}$. (mean 9.9 $\mu\text{U}/\text{ml}$.). 7 of the 14 control children had plasma growth hormone levels of less than 1 ng./ml. In 6 the concentrations ranged from 1-6 ng./ml., and a high fasting level of 17 ng./ml. was recorded in the remaining control child.

In the fasting diabetic children, blood glucose values ranged from 140 mg./100 ml. to 424 mg./100 ml., and in the non-fasting 176 mg./100 ml. to 1820 mg./100 ml. Mean values of insulin in the fasting and in the non-fasting diabetic children were 6 $\mu\text{U}/\text{ml}$. and 10 $\mu\text{U}/\text{ml}$., respectively.

Received 9 July 1969.

TABLE I
Fasting Blood Glucose, Plasma Insulin, and
Growth Hormone Results in the Control Children

Age yr. mth.	Sex	Blood Glucose (mg./100 ml.)	Plasma Insulin (μ U/ml.)	Plasma Growth Hormone (ng./ml.)
2 7	M	71	—	5
4 8	M	64	6	<1
5 0	M	64	5	17
5 4	M	66	5	<1
5 6	F	62	21	2
7 3	F	64	2	5
7 11	F	66	—	<1
8 4	M	63	—	<1
9 1	M	68	14	<1
9 5	F	58	—	<1
9 8	M	56	16	
12 5	F	58	14	
13 0	M	59	11	<1
13 6	M	79	—	2
14 7	F	69	—	6
15 2	M	72	5	1
Mean Range		64·9 56–79	9·9 2–21	<1–17

neither was significantly different from the mean insulin value in the control children ($9\cdot9 \mu\text{U/ml.}$). However, 2 of the diabetic children (Cases 21 and 25) had levels of 29 and $43 \mu\text{U/ml.}$ respectively, exceeding the upper limit of the control group range defined by the mean + 3 SD.

Growth hormone concentrations in the fasting diabetic children were similar to those obtained in the control children, ranging from 1 ng./ml. to 6 ng./ml. Only 1 of the 6 had a value of less than 1 ng./ml. Of the 14 non-fasting, more severely ill diabetic children in whom growth hormone was measured, only 1 had a level of less than 1 ng./ml. Values in the remaining 13 children ranged from 2 ng./ml. to 50 ng./ml., 3 children exceeding the highest level observed in the control group (17 ng./ml.).

Discussion

Plasma insulin levels in the newly diagnosed diabetic children were not significantly different from those obtained in the fasting control children,

TABLE II
Clinical and Biochemical Findings in Diabetic Children

Case No.	yr.	Age mth.	Sex	Clinical Ketosis	Duration of Symptoms (wk.)	Blood Glucose (mg./100 ml.)	Plasma Insulin (μ U/ml.)	Plasma HGH (ng./ml.)
<i>Fasting</i>								
1	2	2	M	—	2	424	7	1
2	3	6	M	—	8	161	3	1
3	4	11	M	—	3	140	1	6
4	5	10	M	—	3	160	12	<1
5	10	2	M	+	2	232	3	1
6	10	11	M	—	5	236	10	4
Mean Range						225·5 140–424	6 1–12	<1–6
<i>Non-fasting</i>								
7	1	8	F	+	1	368	10	29
8	2	9	M	—	1	530	7	—
9	3	6	M	+	6	1820	2	11
10	4	7	F	+	1	600	—	3
11	4	11	M	+	1	556	2	3
12	4	11	F	—	4	462	10	—
13	5	1	F	—	2	176	3	33
14	6	2	F	+	2	370	7	3
15	6	4	F	—	6	308	16	—
16	6	8	F	+	8	288	4	3
17	7	6	M	—	6	432	13	—
18	7	9	M	—	1	282	16	6
19	8	2	F	+	3	592	2	—
20	8	3	F	+	2	880	6	2
21	9	8	M	+	1	560	29	—
22	10	6	F	+	3	404	10	—
23	10	6	F	+	8	596	3	3
24	11	3	F	+	8	320	2	50
25	11	6	F	—	2	652	43	—
26	11	9	M	+	1	416	1	>1
27	11	9	F	+	4	396	8	5
28	13	5	M	+	1	292	17	5
Mean Range						513·6 176–1820	10·0 1–43	<1–50

despite the presence of hyperglycaemia. Hyperglycaemia therefore did not produce the expected increment in plasma insulin concentration. This is in agreement with the findings of Drash *et al.* (1968) and Parker *et al.* (1968) who have suggested that juvenile diabetes mellitus is a consequence of a primary insulin deficiency. Though the hyperglycaemia in the diabetic children in this investigation was not induced by oral glucose, the coexistence of very high blood glucose values and insulin levels in the normal fasting range adequately demonstrated the islet cell insufficiency. However, 2 of the non-fasting diabetic children (Cases 21 and 25) had plasma insulin levels more than 3 SD above the mean control fasting value, suggesting a partial, albeit inadequate, islet cell response. That an insulin response persists in some children at the time of onset of diabetes is supported by the frequent clinical experience of falling exogenous insulin requirements, sometimes to zero, in the period soon after diagnosis (Baker, Kaye, and Root, 1967).

The role of growth hormone in the pathogenesis of diabetes mellitus has been argued since Young (1937) first showed the diabetogenic effect of anterior pituitary extracts. The results presented here suggest that plasma growth hormone concentrations in juvenile diabetes are not much increased, and do not approach the values associated with the development of diabetes in acromegaly.

The less severely ill children who were investigated after overnight fasting had plasma growth hormone concentrations similar to the control children, and only 3 of the more severely ill non-fasted diabetic children had levels greater than the highest recorded in the control group. There is therefore little evidence in our data to support the hypothesis of a causative role for growth hormone in diabetes. However, Hunter and Rigal (1966) have shown that in the 'endocrinologically normal' child growth hormone may be absent from the plasma or too low to measure with available methods for considerable periods during the day. The results obtained in control children reported here were similar. Measurable levels of growth hormone were found in 90% of the diabetic children

indicating a more continuous secretion. Johansen and Hansen (1969) have reported persistently raised secretion of growth hormone in diurnal studies of newly diagnosed juvenile diabetics. Unfortunately they did not comment on the clinical state of their patients. In the children reported here higher growth hormone values were recorded in those who were considered too ill for treatment to be delayed. Jacobs and Nabarro (1969) have reported high levels of growth hormone and a return to normal values with treatment in diabetic adults with severe ketosis. Metabolic derangements and stress in the more severely ill diabetic child may therefore be responsible for the increased growth hormone secretion which then exacerbates the situation through its known diabetogenic effect.

We are indebted to Professor D. V. Hubble for his support, to the Consultant Staff of the Birmingham Children's Hospital for permission to investigate their patients, to the Resident Medical Staff for obtaining some of the blood samples, and to Miss Bernice Morris and Mr. Geoffrey Holder for their expert assistance in the laboratory.

REFERENCES

- Baker, L., Kaye, R., and Root, A. W. (1967). The early partial remission of juvenile diabetes mellitus. *Journal of Pediatrics*, **71**, 825.
- Discombe, G. (1963). An inexpensive method for estimation of true glucose in blood and other fluids by the Autoanalyser. *Journal of Clinical Pathology*, **16**, 170.
- Drash, A., Field, J. B., Garces, L. Y., Kenny, F. M., Mintz, I., and Vazquez, A. M. (1968). Endogenous insulin and growth hormone responses in children with newly diagnosed diabetes mellitus. *Pediatric Research*, **2**, 94.
- Hartog, M., Gaafar, M. A., Meisser, B., and Fraser, R. (1966). Immunoassay of serum growth hormone in acromegalic patients. *British Medical Journal*, **2**, 1229.
- Hunter, W. M., and Rigal, W. M. (1966). The diurnal pattern of plasma growth hormone concentration in children and adolescents. *Journal of Endocrinology*, **34**, 147.
- Jacobs, H. S., and Nabarro, J. D. N. (1969). Plasma 11-hydroxy corticosteroid and growth hormone levels in acute medical illness. *British Medical Journal*, **2**, 595.
- Johansen, K., and Hansen, A. P. (1969). High 24-hour level of serum growth hormone in juvenile diabetics. *British Medical Journal*, **2**, 356.
- Morgan, C. R., and Lazarow, R. (1963). Immunoassay of insulin: a two antibody system. *Diabetes*, **12**, 115.
- Parker, M. L., Pildes, R. S., Chao, K. L., Cornblath, M., and Kipnis, D. M. (1968). Juvenile diabetes mellitus, a deficiency in insulin. *Diabetes*, **17**, 27.
- Young, F. G. (1937). Permanent experimental diabetes produced by pituitary (anterior lobe) injections. *Lancet*, **233**, 372.