The African Journal of MEDICAL SCIENCES

Volume 4

1973

BLACKWELL SCIENTIFIC PUBLICATIONS
Oxford London Edinburgh Melbourne

Afr. J. med. Sci. (1973) **4**, 31–36.

Insulin-Induced Hypoglycaemia in Ugandan Patients with Chronic Pancreatic Disease

Some Preliminary Observations

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(*Received* 30 *March* 1972; *accepted* 14 *June* 1972)

Summary. Proneness to hypoglycaemia while on insulin therapy is a well recognized characteristic of diabetes secondary to chronic pancreatic disease. The studies reported in this paper confirm suggestions from elsewhere that hypoglycaemia in this condition is accompanied by a poor increase in growth hormone concentrations as compared to controls. Since plasma cortisol concentrations in response to hypoglycaemia were not different from those in controls and insulin disappearance rates were also identical with those of controls it is likely that this HGH response is the major difference in these patients. Though this preliminary report will need confirmation by a larger series of observations the possible implications of this feature in this disease are briefly discussed.

Résumé. La susceptibilite a l'hyperglycemie, quand on est sous la therapie d'insuline, est un symptome diacritique du diabete, secondaire a la maladie chronique du pancreas. Les observations soumises en cette dessertation confirment les suggestions trouvees ailleurs, qui indiquent que l'hyperglycemie en cette condition va avec un development minime des concentrations d'hormone pour la croissance, par rapport aux cas temoins.

Puisque les concentrations d'hydrocortisone du plasma ne sont pas differentes en reaction de celles trouvees chez les cas temoins, et vu que le taux de la dispersion d'insuline est identique a celui des cas temoins, il est probable que cette reaction d'hormone pour la croissance fasse la difference principale dans ces cas. Ce sont les implications possibles de cet aspect d'hyperglycemie qu'on va discuter brievement en cet expose: Cependant, il faudra confirmer ce rapport preliminaire en serie d'observations plus elargie.

Pancreatic diabetics have a marked tendency to develop hypoglycaemia while on insulin therapy (Bank, 1966). In South Africa it was shown that when challenged with standard

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doses of insulin in the laboratory they developed a more profound hypoglycaemia from which they recovered more slowly than controls (Joffe, Bank & Marks, 1968). Furthermore, in our laboratory many of them have been shown to maintain normoglycaemia even when they have comparatively low concentrations of serum insulin both in the fasting state and after glucose loading. This sensitivity to insulin has also been remarked upon by other workers (Peters *et al.*, 1966). Though glucagon deficiency has been suggested to be part of the explanation for this (Anguilar-Parada, Eisentrant & Unger, 1969), studies capable of distinguishing pancreatic from enteroglucagon are needed to confirm this. There is also the possibility that insulin is degraded at a slower rate in patients than controls which has not been excluded.

Additional interest was added to the problem by the demonstration that there was poor growth hormone (HGH) production in response to hypoglycaemia in patients with cystic fibrosis of the pancreas (Green, Fefferman & Nair, 1967). A poor growth hormone response to hypoglycaemia has also been demonstrated in diabetics with pancreatic calcification (Vinik *et al.*, 1970). While it is possible that defective HGH production in response to hypoglycaemia is the major defect, a concurrent defect in cortisol production in this setting has not been excluded. Since this would be important to our understanding of the genesis of this phenomenon the position has been studied again and this paper reports on the prelimiary results obtained by studying six patients and seven controls in Mulago Hospital, Kampala, Uganda.

The following parameters have been studied:

(a) Serum growth hormone concentrations in response to insulin-induced hypoglycaemia.

(b) Insulin disappearance rates.

(c) Plasma cortisol concentrations in response to insulin-induced hypoglycaemia.

MATERIALS AND METHODS

Six patients with chronic pancreatic disease were studied. They all gave positive results with the Lundh test procedure (Lundh, 1962; Kajubi & Kyobe, 1970) and they were receiving pancreatic replacement therapy. Two had symptomatic diabetes as well as calcification on abdominal X-rays. All had never had insulin at the time of study.

There were seven controls who were hospital patients recovered from brief acute illnesses not related to the abdomen or endocrine system. They had no calcification on abdominal X-rays and no evidence of disease of the liver or pancreas. All the subjects had normal serum protein concentrations at the time of study.

Insulin hypoglycaemia

After an overnight fast followed by half an hour's rest on a couch, a fasting blood sample was obtained from each subject through an indwelling catheter. Subsequent samples were obtained at 30, 45, 60 and 90 min through the same catheter. Soluble insulin (0·1 unit/kg body weight) was injected intravenously in the opposite arm immediately after obtaining the fasting sample. Plasma glucose was determined by the glucose oxidase method (Marks, 1959) and HGH by the radio-immunoassay method (Pennisi, 1968). Bound was separated from free hormone by filtration on Oxoid filter discs. Cortisol was measured on serum by the technique of competitive protein binding using tritiated cortisol (Murphy, 1967). In two

patients there was so much discomfort during the period of hypoglycaemia that the test was terminated with glucose infusions immediately after the 60th min.

Insulin disappearance rates

These were investigated in four controls and four patients. The blood sampling procedure was exactly the same as that outlined above except that after the insulin injection blood was obtained from the indwelling catheter every 5 min up to and including the 60th min. In one control subject the disappearance of endogenous insulin was also investigated following a

TABLE 1. Plasma glucose and growth hormone concentrations in controls and pancreatic subjects during insulin tolerance tests

	Time (min)						Time (min)					
Patient No	0	30	45	60	90	Maximum rise above fasting figure	0	30	45	60	90	Maximum fall below fasting figure
Pancreatics												
553	2	10	10	12	10	10	63	34	19	20	31	44
554	3	20	37	34	18	34	64	38	35	39	52*	29
555	1	6	6	14	15	14	62	45	32	40	45	30
602	2	7	10	14	8	12	65	15	28	70	94*	50
606	6	20	31	27	32	26	53	30	33	22	39	31
613	0	0	20	19	18	20	77	37	39	53	53	40
Mean	2·2	10·5	19·0	20·0	17·0	19·3	64·0	33·1	31·0	40·6	52·3	37·3
SEM	1·2	4·0	4·5	3·0	3·2	3·0	3·1	4·1	2·8	7·7	8·9	4·2
Controls												
564	1	12	34	55	79	78	56	26	45	56	62	30
565	2	28	27	29	29	27	65	23	29	40	66	42
576	1	15	45	78	28	77	71	21	33	56	53	50
579	1	16	16	32	15	31	55	48	41	35	21	34
583	0	45	47	42	35	47	63	40	28	32	50	35
598	2	42	38	12	9	40	74	35	25	29	41	49
569	0	21	26	24	10	26	73	39	47	47	53	34
Mean	1·0	25·5	33·2	38·8	29·2	46·4	65·2	33·1	35·4	42·1	49·4	39·1
SEM	0·9	5·0	4·1	8·2	9·1	7·1	2·9	3·8	3·3	4·2	5·6	5·0
p(V's patients)	NS	0·05 (Significant)	NS	NS	NS	0·01 (Significant)	NS	NS	NS	NS	NS	NS

* Test discontinued by a glucose infusion at the 60th min.

maximal intensive beta cell stimulus consisting of oral glucose plus a combined injection of glucagon and tolbutamide as first described by Ryan and others (Ryan, Nibbe & Schwartz, 1967). Serum insulin concentration was measured by the radio-immuno-assay technique (Hales & Randle, 1963), and bound was separated from free hormone by filtration on oxoid filters. Insulin concentrations were then plotted on semilog paper against

time. Half-times were then deduced from the plot (Samols & Marks, 1966; Oskor & Christensen, 1966).

RESULTS

HGH responses

These are shown in Table 1. The fasting concentrations were similar in patients and controls. The mean concentrations were, however, higher in controls at 30, 45, 60 and 90 min but the difference was only statistically significant ($P = 0{\cdot}05$) at the 30th min. In both patients and controls there was no uniform point in time when they reached their maximal concentrations; it varied from 30 to 90 min; but the mean increment above the fasting concentrations (which is a measure of the *change* induced by the stimulus of hypoglycaemia) achieved by the controls was significantly higher ($P = 0{\cdot}01$) than that shown by the patients.

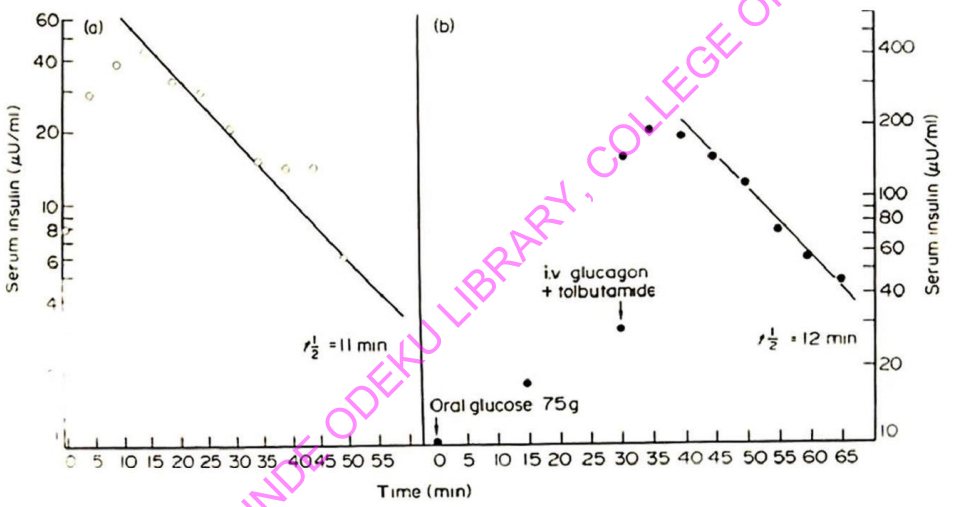

FIG. 1. Insulin disappearance rates. (a) After a bolus infusion of soluble insulin (exogenous). (b) After an intravenous injection of glucagon (1 mg) + tolbutamide (0·5 g) 1/2 hr after oral glucose (endogenous).

Plasma glucose responses

These are also shown in Table 1. Hypoglycaemia (below 40 mg/100 ml) was achieved in all the subjects, but the glucose concentrations reached by the patients were not different from those of controls. The mean differences between the lowest and fasting concentrations were also not different between the two groups.

Insulin disappearance rates

The half times for exogenous insulin obtained in the four controls were 12, 9, 8 and 11 min and in the four patients were 9, 11, 13 and 12 min. The results of endogenous insulin in the one control subject are shown in Fig. 1. It is interesting that they were practically the same for both endogenous and exogenous insulin. They are also in agreement with those

obtained by Samols & Marks (1966) and by Oskor & Christensen (1966) who used similar testing procedures in non-African subjects.

Plasma cortisol responses

These are shown in Table 2. There was no difference between the responses of patients and those of controls. Results of this test have not been reported on in East Africa. Although the absolute concentrations of cortisol reported here are slightly lower, the maximum increments above the fasting concentrations are similar to those reported in Nigerians (Adadevoh, 1968). This situation may be accounted for by the different method of assay of cortisol used in this paper.

TABLE 2. Mean concentrations of plasma cortisol (μg/100 ml) ($\pm$SEM) in pancreatic and control subjects during insulin tolerance tests

	Time (min)					
	0	30	45	60	90	Approximate mean increment above fasting value
Pancreatics	13·9 $\pm$ 1·6	20 $\pm$ 2	18·6 $\pm$ 2·8	16·0 $\pm$ 2·8	17·7 $\pm$ 3	7·1
Controls	12·9 $\pm$ 3	17·9 $\pm$ 4·6	17·2 $\pm$ 2·4	19·6 $\pm$ 3·6	17·7 $\pm$ 2·3	6·7

DISCUSSION

Except for the fact that two of the patients had to have their tests stopped at the 60th min because of severe symptoms the results obtained in this study do not support the reported occurrence (Joffe *et al.*, 1968) of a more severe hypoglycaemia in these patients. The observed glucose concentrations were comparable in the two groups of subjects. The studies were not prolonged for long enough to learn about the possible presence of a delay in recovery in these subjects.

The results support the suggestion of Vinik *et al.* (1970) that the patients show a diminished capacity to increase growth hormone concentrations in response to the stimulus of hypoglycaemia. Furthermore, though the degrees of hypoglycaemia reported in this paper were similar in patients and controls, the observed increments in HGH concentration were poor in the patients.

Plasma cortisol responses were similar in the two groups of subjects as were the observed increments above the fasting values. Insulin degradation rates were also very similar for the two groups and it is significant that all these values were similar to that obtained with the patient's own insulin. They are thus physiologically meaningful.

It appears that the situation represents an isolated pituitary or hypothalamic alteration rather than a generalized one. The ACTH/adrenal relationship appears to be unaltered.

The stimulating effect which glucagon appears to have on HGH production (Mitchell, Byrne & Sanchez, 1970; Cain, Williams & Dluhy, 1970) may be related to the present situation. Since glucagon production is stimulated by hypoglycaemia (Ohneda *et al.*, 1969) its absence consequent upon damage to the pancreatic islets in pancreatic disease would

appear to explain these findings. While this thesis is acceptable to some, others hold that these observations are made with doses of glucagon which are higher than the physiological ones. This point will await further study for its clarification. Furthermore, it would be difficult to sustain this thesis in the case of cystic fibrosis of the pancreas where islet cell damage (and diabetes) is so uncommon.

This feature of chronic pancreatic disease will need to be confirmed by more extensive studies but it may be related to the other puzzling features of pancreatic diabetes such as the relative uncommonness of ketosis.

ACKNOWLEDGMENTS

I am grateful to the International Atomic Energy Agency for financial support and to my Colleagues in Mulago Hospital for allowing me to study patients under their care. I also thank Dr Peter Lunn of the MRC Child Nutrition Unit who estimated the plasma cortisol for me.

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