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Serum Insulin in Ugandan Africans

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Summary. Twenty-six controls, twenty-three patients with chronic pancreatitis and eight with late onset diabetes were studied for serum insulin response to oral glucose loading. Levels of fasting serum insulin in Ugandan Africans were not different from those seen elsewhere. Approximately 43% of the controls and pancreatitis patients had the genetic diabetes pattern of insulin response. It is noted that patients with pancreatic diabetes may have the diabetic gene as well, and may thus be indistinguishable from genetic diabetics in behaviour and type of complications. This finding may explain some of the previously puzzling features of pancreatic diabetes.

Résumé. On a étudié l'insulinémie après surcharge glucosée par voie orale chez 26 personnes normales constituent un groupe de control, chez 23 patients avec une atteinte chronique du pancréas et chez 8 personnes qui présentèrent par la suite du diabète. L'insulinémie, avant la prise d'un repas, fut trouvée a un niveau comparable à celui que l'on trouve dans d'autres pays. A peu près 43% de l'effectif du groupe de control et des patients avec une atteinte pancréatique présentèrent une résponse insulinique comparable à celle des diabétiques génétiques. On remarque que les patients avec un diabète associé à une maladie pancréatique pouvaient tout aussi bien avoir des caractéristiques génétiques de type diabétique et ainsi pouvaient être indiscernables du diabète d'origine génétique aussi bien dans les manifectations que dans le genre de complication. Ces faits pouvaient expliquer quelques unes des étranges manifestations du diabète pancréatique.

Using the rat diaphragm method of insulin assay it was reported that atypical insulin-like activity (ILA) was as high in non-obese Ugandan Africans as in obese people in London (Fraser, Saaman & Shaper, 1966). The explanation for this was not clear but it was suggested that the high carbohydrate intake of the Ugandan African stimulated this increased insulin production. Since the rat diaphragm method has been superseded by the radioimmunoassay technique it was decided to investigate the position once more using this latter technique.

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Control subjects were studied in the initial stages of this work but it became apparent that the results may have relevance to subjects suffering from chronic pancreatic disease (Shaper, 1960), with or without diabetes. Patients with this disease were therefore studied in addition to the controls. Eight patients with idiopathic adult onset diabetes were also studied.

MATERIALS AND METHODS

All subjects had been taking a hospital diet which provides about 500 g of carbohydrates/day for at least 3 days. All had never had insulin before.

Controls

Twenty-six adults already recovered from mild illnesses not related to the abdomen who were fit for discharge were studied. They were well nourished and had neither pancreatic calcification on abdominal X-rays nor steatorrhoea. They were selected at random, the only criterion being that of adequate nutrition. They all gave informed consent. Their age range was 21–45 years and their body weight 50–65 kg. There were twelve females and fourteen males.

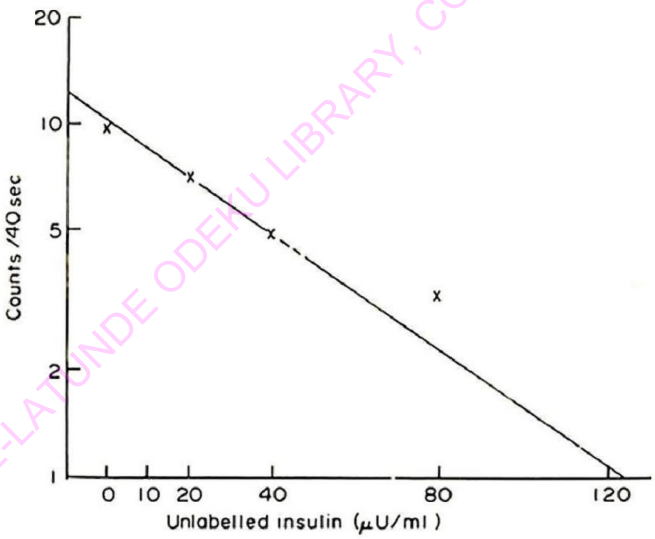

FIG. 1. Radio-immunoassay of serum insulin. Plot of counts (thousands/40 sec) obtained from the standards.

Pancreatic disease patients

The diagnosis was based on pancreatic calcification on abdominal X-rays (eight patients), laparatomy and biopsy findings (three patients), and steatorrhoea associated with abnormal pancreatic function tests (Lundh, 1962; Kajubi & Kyobe, 1970) and normal function tests of the liver and small bowel (twelve patients). Some of the patients in this group had lost weight and had features of malnutrition. Five were symptomatic diabetics. Their age range was 25–40 and body weight between 45 and 60 kg. There were five females and eighteen males.

Adult onset (idiopathic) diabetes

Eight adults were studied. They had no pancreatic calcification and no steatorrhoea. Exocrine pancreatic function tests were normal. All had been controlled on tolbutamide therapy which was stopped at least 3 days before the tests. The fifth patient was the daughter of the fourth subject. Their ages ranged between 20 and 40 years and body weight 52–70 kg. There were three females and five males.

Each subject was fasted overnight and venous blood was obtained before they took 50 g of glucose in 300 ml of tap water, and 30, 60, 90, 120 and 150 min afterwards. Blood glucose was estimated by the glucose oxidase method (Marks, 1959), and serum insulin by the radio-immunoassay technique of Hales & Randle (1963), as modified by the Radiochemical Centre, Amersham, England (Technical Bulletin 69/4) from whom the entire kit for the assay was obtained. The anti-insulin serum is prepared against ox insulin but in the procedure used it would work with equal sensitivity to ox, human and pig insulin. Calibration was by means of standards of 0, 10, 20, 40 and 80 μU/ml permitting readings of up to 110–130 μU/ml, to be obtained (Fig. 1). Where the insulin concentration was beyond this range the assay was repeated with the serum diluted appropriately.

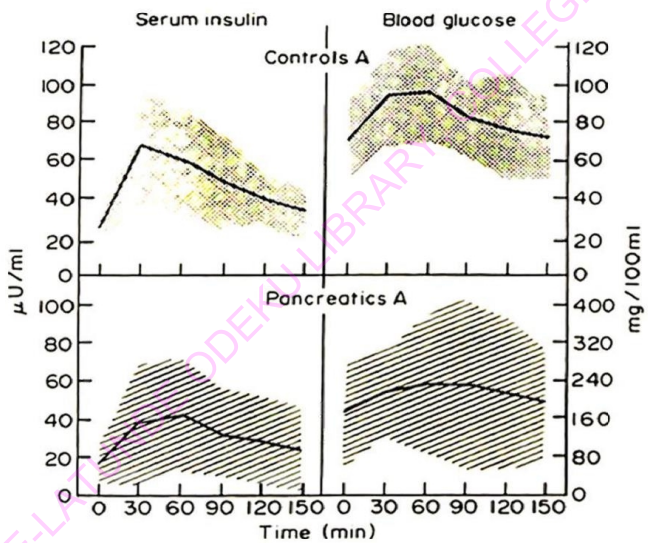

FIG. 2. Mean concentrations (±SEM) of serum insulin and plasma glucose in controls A and pancreatics A in response to oral glucose loading at time zero.

RESULTS

The accompanying Figs. (2–4) and Table 1 show the mean (±SEM) serum insulin and plasma glucose levels of all the subjects. The overall fasting level of serum insulin in controls was 25±6·7 μU/ml. Values of 6–27 μU/ml (Hales & Randle, 1963; Berson & Yalow, 1960), have been obtained in Britain and the U.S.A. respectively.

However, detailed examination of the serum insulin responses in the control subjects showed that there were two types of response. Type A reached a peak within the first

60 min and returned to a value near the fasting value by the end of the test. The B type of response reached a peak at about the 90th min or later and by the 150th min the level of insulin was still slightly elevated when compared to the fasting value. Patients with pancreatic disease also showed one of the two types of response referred to above.

The mean serum insulin levels in pancreatic patients tended to be lower than those of

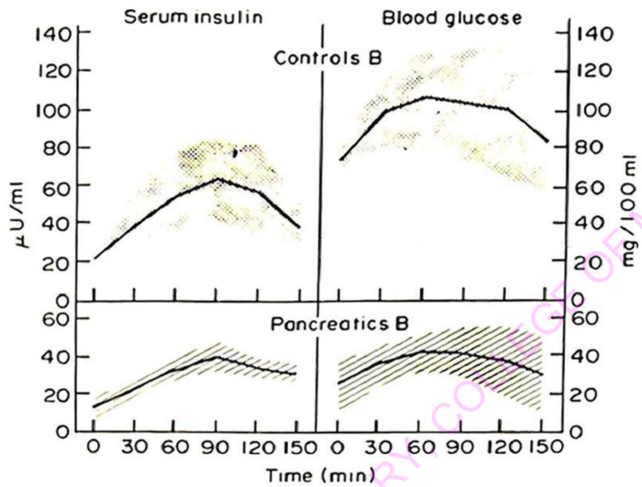

FIG. 3. Mean concentrations (±SEM) of serum insulin and plasma glucose in controls B and pancreatics B in response to oral glucose loading at time zero.

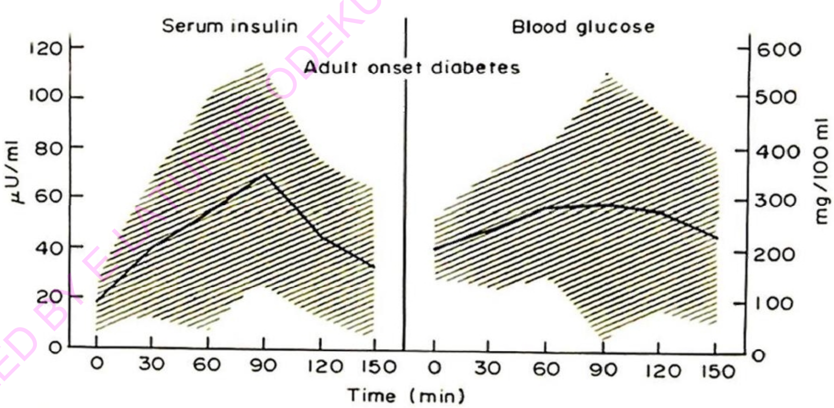

FIG. 4. Mean concentrations (±SEM) of serum insulin and plasma glucose in patients with idiopathic diabetes.

controls. This was true for both A and B types. This difference was statistically significant ($P<0{\cdot}02$, except at the 150th min where $P<0{\cdot}1$) in the case of the B but not the A group of pancreatic patients. The B group of pancreatics showed values with the smallest scatter around their means.

Of those with adult onset diabetes, six had the B type of response and two had so feeble a rise as to make classification of it impossible. However, the overall response for this group was of the B type pattern.

The mean plasma glucose levels tended to be higher in patients with pancreatic disease than in controls but this difference was not statistically significant.

TABLE 1. Mean concentrations (± SEM) of serum insulin and plasma glucose after glucose loading in twenty-six controls, twenty-three patients with pancreatic disease and eight with idiopathic disease

Patients	Time (min)											
	Serum insulin (μU/ml)						Blood glucose (mg/100 ml)					
	0	30	60	90	120	150	0	30	60	90	120	150
Controls A (fifteen patients)	25·0 ± 6·7	69 ± 32	60·7 ± 31·5	49·0 ± 28·6	40·2 ± 16·3	34·0 ± 14·9	71·7 ± 19·9	96·0 ± 27·3	97·6 ± 27·5	84·9 ± 22·5	78 ± 30	73·4 ± 20·8
Pancreatics A (twelve patients)	16·2 ± 11·0	37·5 ± 32·4	42 ± 30	31·6 ± 23·8	28 ± 24	24·0 ± 22·2	134·0 ± 115·8	176·2 ± 94·5	198 ± 136	192·5 ± 176·0	177·6 ± 163·0	156 ± 163
Controls B (eleven patients)	22·0 ± 6·4	40·3 ± 20·3	55·3 ± 24·3	65·2 ± 22·5	58·5 ± 25·8	39·7 ± 15·0	75·8 ± 11·5	100·6 ± 18·3	108 ± 29	106·0 ± 31·6	102·0 ± 36·7	84·8 ± 30·4
Pancreatics B (eleven patients)	10·2 ± 7·0	21·6 ± 4·6	32·2 ± 5·9	40·2 ± 9·3	33·5 ± 5·2	30·2 ± 6·7	98·8 ± 53·4	138·5 ± 46·0	168 ± 43	164 ± 55	147·9 ± 73·0	116·6 ± 88·0
Adult onset diabetics (eight patients)	17·5 ± 12·0	41·0 ± 28·6	55·6 ± 47·7	71·6 ± 45·7	46·0 ± 33·5	34·0 ± 30·2	206 ± 157	246 ± 117	287·5 ± 135·0	295 ± 274	280 ± 250	239 ± 189

DISCUSSION

This study shows that the levels of immunoreactive insulin in Ugandans are in the same range as those found by workers in North America and Europe. The finding of higher levels of biologically active insulin-like material previously reported is difficult to interpret because insulin-like activity detected by the rat diaphragm method is not all due to immunoreactive insulin. The suggested explanation that these high levels would be a consequence of a high carbohydrate diet in the Ugandan is untenable if it implies that the high protein, low carbohydrate diet of Londoners is a comparatively poor stimulus of insulin secretion. Proteins are also potent stimulants of insulin release (Floyd *et al.*, 1966) and the rise in plasma insulin that occurs when carbohydrate and protein are taken together by mouth is more than the sum of their individual contributions (Rabinowitz *et al.*, 1966).

Since the introduction of the technique of insulin immunoassay it has been possible to

examine the pattern of insulin release in response to oral glucose in many subjects. Two major abnormalities in beta-cell response in genetic diabetes have been revealed. First, the insulin response is sluggish, the so called 'beta-cell inertia', so that the peak of insulin output comes at 90 or 120 min instead of 30–45 min as in the normal person (Davidoff, 1968). The second one is a smaller than normal insulin output in response to a given insulinogenic stimulus. It has been further suggested that the sluggish response allowed blood glucose to rise to a high level which then stimulated further insulin release leading to the late and high peak of insulin output seen in genetic diabetes (Davidoff, 1968). This pattern of insulin response is usually obtained in asymptomatic individuals with a strong family history of diabetes and in mild genetic diabetics with fasting blood sugars of 150 mg% or less. Severe diabetics have often been found to have limited endogenous insulin output (Seltzer *et al.*, 1967). The delayed peak response is thus the hall mark of genetic diabetes.

Eleven of the twenty-six controls in this study (42%) had the genetic diabetes type of response. This cannot be taken to indicate the overall frequency of the diabetic gene in this country because these were hospital patients who were as such a selected group of subjects. Moreover, the patients belonged to different tribes and no attempt has been made to separate them into tribal groups. It however, suggests that the gene is not uncommon. The Diabetic Clinic at Mulago Hospital, Kampala, has approximately 800 diabetics attending regularly at the present time. The hospital serves a population of about one-and-half million people living within a 30-mile radius of Kampala, the major city of Uganda.

Of the twenty-three patients with chronic pancreatitis, eleven (47%) had the genetic diabetes type of response. This is interestingly a similar frequency to that of the controls. The fasting levels of insulin in this group were generally lower than in the controls and those in the B group were significantly so. Furthermore, the overall insulin values in the B group showed far less scatter around their means than in the A group. The comparatively low levels of insulin in this group are a consequence of the fact that damage to the pancreas must compromise the beta-cell pool quantitatively, thus limiting the insulin producing capacity of these patients. This has, indeed, been shown by work done elsewhere (Joffe *et al.*, 1968). It appears now that the presence of the diabetic gene is an additional limitation to the functioning capacity of the beta-cells of these patients.

It is also interesting to note that many of the pancreatic disease patients with comparatively low insulin levels were not symptomatic diabetics but maintained normal blood sugar levels. This must mean that they have increased sensitivity to insulin as compared to controls. This would be consistent with the fact that those with frank diabetes often go into hypoglycaemia on what would otherwise be standard doses of exogenous insulin (Duncan, McFarlane & Robson, 1958; Bank, 1966).

This study also shows that patients with pancreatic diabetes may have the gene for diabetes. This is not surprising since pancreatitis is an acquired condition. This means that a given patient with diabetes and pancreatic calcification may behave like a genetic diabetic in his pattern of insulin release and in his response to therapy. This may explain in part some of the higher than normal rises in insulin levels which have been reported with oral glucose (Bank *et al.*, 1968), and may be the explanation in some of the cases of pancreatic diabetes who are controlled on tolbutamide therapy. It is however, clear that the extent of damage to the beta-cell mass of the pancreas is a very important determinant of the magnitude of insulin rise obtainable in this class of patients. Thus, one of the patients with

pancreatic calcification in this series did not have diabetes and his insulin response was indistinguishable from that of controls. It was an A type of response. The extent of damage was presumably limited in this case.

It can also be assumed from this that the controversial suggestion that the renal and retinal/vascular complications of diabetes develop only among genetic diabetics (Le Compte, 1957) is not necessarily refuted by reports of cases of pancreatic diabetes who have developed these complications (Duncan *et al.*, 1958, McCullagh, Cooke & Shirley, 1958). It could very well be argued that these were patients with the diabetic gene who would have developed the disease and its complications anyway. The application of insulin immunoassay to this point may help clarify our thinking on this problem.

The responses observed among adult onset diabetics in this study concur with what would be expected from the work discussed earlier in this paper. The insulin response pattern which they show suggests that they were genetic diabetics.

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