Insulin Secretion in Bantu with Siderosis or Hepatoma*

ELIZABETH J. P. DE BRUIN, *Life Sciences Division, Atomic Energy Board, Pretoria,* AND B. J. MEYER, *Department of Physiology, Medical School, University of Pretoria*

SUMMARY

The IR and concomitant GTC was evaluated in 10 siderotic Bantu patients and in 11 Bantu patients suffering from hepatoma. A normal IR was found in the siderotic Bantu, occurring, however, at much higher blood glucose levels than those of the control Bantu group. This relatively low IR is ascribed to impaired secretion of the β-cells, due most probably to significant low deposits in the pancreas. A similar relatively low IR in the presence of elevated blood glucose levels was found in the patients suffering from hepatoma. Their IR was furthermore delayed, possibly due to impaired destruction of insulin by the damaged liver. Since these patients were seemingly not siderotic, their relatively low IR apparently cannot be ascribed to iron deposits in the pancreas. It could, however, be due to exhaustion of the β-cells caused by the persistent hyperglycaemia observed in the patients with hepatoma.

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The liver occupies a key position in carbohydrate metabolism and disturbances are encountered in almost all forms of hepatic dysfunction. Impairment of glucose tolerance in liver disease has been frequently reported,[1,2] but few studies have included measurements of serum insulin and where such studies were carried out the results are contradictory.[3-5] Insulin responses in patients with cirrhosis and haemochromatosis have been reported, but to our knowledge no studies have been reported on the insulin responses in patients with siderosis or hepatoma. A study was therefore undertaken to investigate the effect of siderosis and hepatoma on glucose and insulin secretion and the results of the investigation are reported in this article.

MATERIALS AND METHODS

Siderosis

The glucose tolerance test and its impact on insulin secretion was investigated in a group of 10 Bantu males from H. F. Verwoerd Hospital, Pretoria, who were diagnosed as siderotic after liver biopsy. Their ages ranged from 40 to 65 years. Only 3 of these patients had cirrhosis as well.

Hepatoma

Similar glucose and insulin studies were carried out on a group of 11 Bantu males from H. F. Verwoerd Hospital, in whom a diagnosis of hepatoma was made after liver biopsy. Their ages ranged from 37 to 65 years.

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Control Group

A group of 25 Bantu males served as controls. These subjects were drawn from the staff of the Institute for Pathology, Pretoria, and from the staff of the South African Iron and Steel Industrial Corporation, Pretoria, and also included extremely fit employees from the Chamber of Mines, Johannesburg. Their ages ranged from 20 to 60 years.

After an overnight fast, blood samples were taken for determining fasting glucose and insulin values; 50 g of glucose was then given orally and venous blood samples were taken every 30 minutes over a period of 150 minutes (120 minutes in the case of the control group). In addition to investigating the glucose tolerance and insulin response the following parameters were also evaluated: blood cell counts, haematocrit, haemoglobin concentration, plasma electrolytes (K^+, Na^+, Cl^-, HCO_3^-) liver function, plasma proteins and a complete lipogram.

Glucose was determined in a standard Technicon Auto-Analyzer by means of reduction of potassium ferricyanide as originally described by Hoffman[6] and serum insulin according to the double-antibody method of Hales and Randle.[7]

STATISTICAL ANALYSIS

Mean and standard deviations for insulin and glucose were calculated for each group of subjects. In the case of the experimental subjects the median values are also presented since outliers influenced the averages significantly, there being a wide range, especially of insulin values, at any one sampling time and the data thus do not have a normal distribution. The correlation coefficient for the insulin response (IR) and concomitant glucose tolerance curve (GTC) were calculated for each group and tested for significance at the 5% level of reliability ($P<0{\cdot}05$).

RESULTS

Siderosis

The IR and concomitant GTC of the siderotic Bantu are presented in Table I and Fig. 1. A significant correlation between the IR and concomitant GTC was found in

TABLE I. INSULIN RESPONSE AND CONCOMITANT GTC OF SIDEROTIC BANTU

Subject No.	Insulin (μU/ml serum) at: Fasting	30 min.	60 min.	90 min.	120 min.	150 min.	Glucose (mg/100 ml blood) at: Fasting	30 min.	60 min.	90 min.	120 min.	150 min.
1	11	89	61	70	10	7	136	136	118	149	105	
2	9	15	25	46	44		83	101	112	117	117	
3	20	49	62	40	97	91	93	112	112	93	128	
4	16	37	25	34	27		90	169	195	205	175	
5	20	80	78	52	37	19	95	187	214	151	121	82
6	23	98	147	78	34		105	157	153	121	104	
7	9	11	13	16	15	15	85	112	145	174	187	194
8	8	15	19	1	2	3	90	142	162	169	150	125
9	13	53	72	39	34	17	66	121	144	118	106	70
10	13	51	66	38	23	15	77	155	180	148	100	85
Mean	14·20	49·80	56·80	41·40	32·30	23·86	92·00	139·20	153·50	144·50	129·30	111·20
SD	5·31	31·40	39·88	22·71	26·20	30·15	18·72	27·94	35·00	33·11	31·09	50·70
Median	14	50	61·5	39·5	30·5	15	90	139	149	148·5	119	85

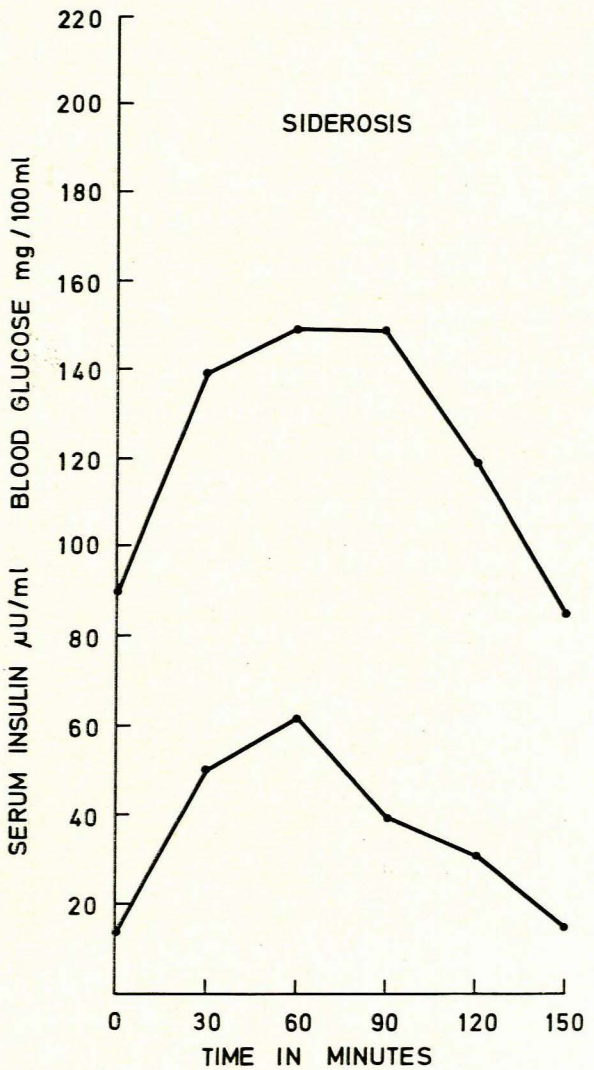

Fig. 1. Graphic representation of the IR and concomitant GTC of siderotic Bantu: median values.

60% of these patients. Although their IR were within the normal range as compared to the IR of the control group, 3 of the patients exhibited a diabetic GTC. The GTC was furthermore delayed with a peak at 60 minutes, returning to the fasting value only at 150 minutes; in 5 of the subjects the glucose level was not determined at 150 minutes, but only up to 120 minutes. Two of the patients showed a steady incline in their insulin levels concomitant with a slow incline in their glucose levels, neither of which returned to the fasting level after 120 or 150 minutes.

Hepatoma

The IR and concomitant GTC of Bantu suffering from hepatoma are presented in Table II and Fig. 2. Their insulin values were relatively low for their concomitant high blood glucose levels and the insulin curve showed a delayed peak and only tended to decline at 150 minutes. Even though 45% of the subjects showed a correlation between their IR and concomitant GTC, their insulin values were much lower than is to be expected for such high glucose levels; 6 of the patients showed a diabetic GTC while the other 5 had sustained high blood glucose levels at 150 minutes.

Control Group

The IR and concomitant GTC values of the control group are presented in Table III and Fig. 3. A significant correlation between the IR and concomitant GTC was found in only 32% of the subjects. Except for the fasting insulin value, the mean IR of the Bantu did not differ significantly from the recommended values for the IR in Caucasians.[8] The GTC of the Bantu was significantly lower than that of the suggested normal values for Caucasians at fasting, at 30 minutes and at 60 minutes. Our control group, however, consisted of only 25 Bantu subjects taken at random.

TABLE II. INSULIN RESPONSE AND CONCOMITANT GTC OF BANTU WITH HEPATOMA

Subject No.	Insulin (μU/ml serum) at: Fasting	30 min.	60 min.	90 min.	120 min.	150 min.	Glucose (mg/100 ml blood) at: Fasting	30 min.	60 min.	90 min.	120 min.	150 min.
1	11	25	23	44		30	110	139	229	263		284
2	23	75	69	83	114		109	150	195	219	218	
3	12	22	59	43	56		98	160	193	179	179	
4	6	9	19	19	17	17	60	80	104	130	136	123
5	9	12	13	14	6	12	121	160	194	223	250	275
6	18	23	31	75	97	97	122	150	192	243	243	221
7	13	27	36	42	51	42	—	109	137	145	142	128
8	14	25	41	44	42	29	91	137	184	186	178	145
9	17	50	152	173	24	108	78	113	138	145	142	136
10	12	72	81	97	82	87	73	109	136	162	159	147
11	26	32	47	50	180	39	59	82	117	128	127	116
Mean	14·64	33·82	51·91	62·18	66·90	51·22	92·10	126·27	165·36	183·91	177·40	175·00
SD	5·94	22·29	39·34	44·57	52·89	36·21	23·71	29·24	40·11	46·98	45·12	66·70
Median	13	25	41	44	53·5	39	94·5	137	184	179	168·5	145

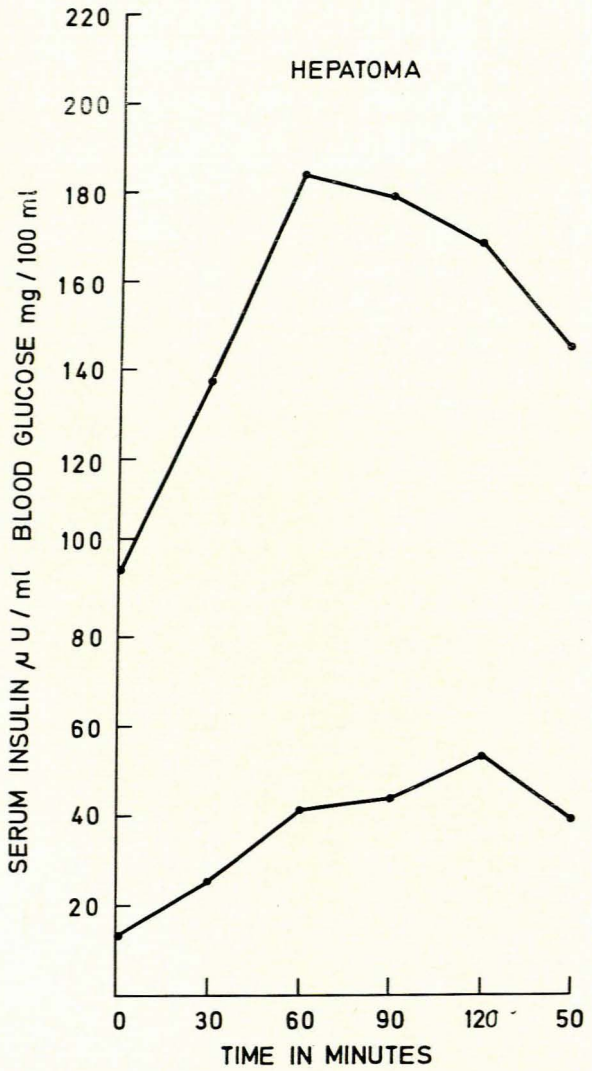

Fig. 2. Graphic representation of the IR and concomitant GTC of Bantu suffering from hepatoma: median values.

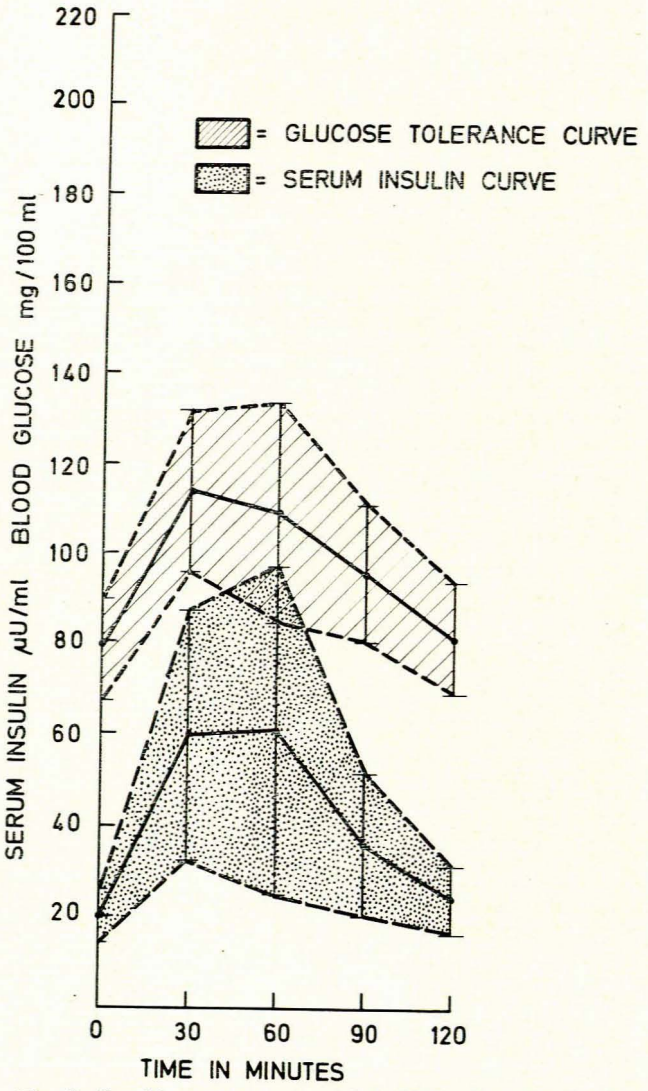

Fig. 3. Graphic representation of the IR and concomitant GTC of normal Bantu: mean values and standard deviations.

TABLE III. THE INSULIN RESPONSE AND CONCOMITANT GTC OF THE BANTU CONTROL GROUP

Subject No.	Insulin (μU/ml serum) at: Fasting	30 min.	60 min.	90 min.	120 min.	Glucose (mg/100 ml blood) at: Fasting	30 min.	60 min.	90 min.	120 min.
1	24	73	73	25	22	90	125	116	90	85
2	19	44	57	68	27	76	110	106	106	67
3	12	35	29	31	18	90	105	98	98	80
4	19	88	160	29	21	90	137	123	80	71
5	22	54	83	57	35	90	141	153	123	102
6	20	52	46	19	19	71	109	98	90	62
7	3	51	28	21	7	85	105	75	80	62
8	18	24	30	24	16	75	80	95	90	80
9	18	53	45	35	22	70	90	90	95	70
10	20	57	36	26	15	75	80	95	75	70
11	16	51	45	29	23	60	115	115	90	99
12	18	35	31	31	37	70	99	85	80	80
13	19	34	43	35	28	75	111	120	111	105
14	21	53	98	60	29	95	141	156	111	81
15	33	113	77	47	31	99	130	111	102	95
16	22	43	26	30	37	81	111	95	105	81
17	16	70	69	27	21	90	102	90	95	75
18	18	58	42	32	25	75	100	61	65	70
19	25	60	27	30	21	80	112	115	90	97
20	29	103	66	45	33	61	131	131	129	100
21	21	33	91	33	27	57	106	80	100	80
22	29	96	124	82	36	90	124	129	115	90
23	18	43	35	24	19	80	115	115	94	83
24	25	136	131	46	20	83	146	152	106	79
25	16	45	41	19	19	65	129	131	80	83
Mean	20·04	60·16	61·32	36·20	24·32	78·92	114·16	109·40	96·00	81·88
SD	5·88	27·51	36·17	15·94	7.60	11·37	17·96	24·39	15·24	12·36

DISCUSSION

In view of the important role of the liver in the regulation of the blood glucose level, it is not surprising that a decreased tolerance to an oral or intravenous glucose load is frequently present in patients with liver disease.[1,9] Impaired glucose tolerance was observed in 7 of the siderotic patients and in all of the hepatoma patients. *In vitro* data have indicated that a number of factors such as impaired glycogenesis,[9,10] a diminished effective hepatic blood flow[11] and a defective peripheral glucose uptake[12] may be involved in this 'hepatic diabetes'. The over-all role of insulin in this scheme is not known and has been difficult to assess because of problems involved in its measurement. Although a normal blood glucose response to intravenous tolbutamide in patients with liver disease who have abnormal oral glucose tolerance may be considered presumptive evidence that insulin secretion is normal,[13] more direct proof of this has been lacking.

Whether an excess of iron modifies insulin secretion to any degree is also not known. It has, however, been suggested that the presence of iron in the portal tracts might provoke fibrosis or cirrhosis, especially in the presence of chronic malnutrition.[14] Since a few of the patients had cirrhosis as well, the latter condition may have influenced their IR. Berkowitz[4] found a high IR in cirrhotic patients in contrast to Hernandez *et al.*[3] who found a normal IR, occurring, however, at higher blood glucose levels. The findings in the present study are consistent with those of Hernandez *et al.*[3] except for the 3 subjects who exhibited a flat GTC. The relatively low IR can possibly be ascribed to an impaired secretion of the β-cells, since it is most likely that significant iron deposits were present in the pancreas.[15]

Since the liver removes up to 50% of the insulin during a single passage[16] it might be anticipated that the hepatic uptake of insulin would be impaired in subjects with hepatoma, thus permitting a greater amount of insulin to appear in peripheral blood. However, the observed relatively low and delayed IR in the presence of elevated blood glucose levels may be interpreted as meaning that the β-cells of these patients had an inadequate response similar to that of siderotic patients, and that the delayed insulin curve was due to impaired destruction of insulin by the damaged liver.

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