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Hyperinsulinaemia in non-cirrhotic haemochromatosis: impaired hepatic insulin degradation?

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Summary. This study investigated early alterations of glucose metabolism in idiopathic haemochromatosis. Circulating concentrations of glucose, insulin, C-peptide, glucagon, and gastric inhibitory polypeptide (GIP) were measured after a 100-g oral glucose load in 10 men with idiopathic haemochromatosis in the non-cirrhotic stage of the disease. All had normal glucose tolerance and normal body weight. Ten matched healthy subjects were studied as controls. Insulin concentrations increased to significantly higher levels in patients with idiopathic haemochromatosis than in the control subjects from 30 to 180 min after the glucose load ($p \leqslant 0.01$), while fasting insulin concentrations were not significantly different ($p > 0.05$). Concentrations of glucose, glucagon, C-peptide, and GIP were not significantly different at any time ($p > 0.05$). Thus, patients with idiopathic haemochromatosis show hyperinsulinaemia and hence insulin resistance without impaired glucose tolerance in the non-cirrhotic stage. Since pancreatic insulin secretion (C-peptide), glucagon secretion, and the entero-insulinar axis (GIP) are not impaired in these non-cirrhotic patients with idiopathic haemochromatosis, iron accumulation in the hepatocytes may be responsible for the impaired insulin effect and may cause impaired hepatic insulin extraction.

Key words: Hyperinsulinaemia, insulin resistance, insulin degradation, haemochromatosis, cirrhosis, insulin, glucagon; C-peptide, gastric inhibitory polypeptide.

Diabetes mellitus is one of the classical clinical features in idiopathic haemochromatosis (IHC). The cause of the close association between hyperglycaemia and IHC, however, remains uncertain. Damage to pancreatic islets by iron deposits in β cells, genetic predisposition, and hepatic cirrhosis are thought to be the main factors causing diabetes mellitus in IHC [1–4]. Diabetes mellitus and impaired glucose tolerance are also frequent features of other chronic liver diseases [5–6]. Since insulin resistance is a major cause of impaired glucose tolerance in other chronic liver diseases [6–9], it might also be responsible for the impaired glucose tolerance associated with IHC. However, this hypothesis has not been substantiated or refuted so far. This study investigated early alterations of glucose metabolism in IHC: circulating concentrations of glucose, insulin, C-peptide, glucagon, and gastric inhibitory polypeptide (GIP) were measured following an oral glucose load in a homogeneous group of non-cirrhotic IHC patients and were compared with those of matched healthy control subjects.

Subjects and methods

Subjects

Ten men with idiopathic haemochromatosis were studied. The clinical data are shown in Tables 1 and 2. The diagnosis was proved in all cases by: (1) histology of liver biopsy; (2) histochemical or chemical determination of iron excess in liver tissue; (3) documentation of abnormal serum concentrations of iron, transferrin, and ferritin; (4) exclusion of other liver diseases, such as that due to alcohol. Most patients had further strong evidence of IHC by determination of HLA antigens and family history (Table 2). In seven patients, additional biopsies of the intestinal mucosa were evaluated for iron content. Five of the seven patients had increased iron deposits in the intestinal mucosa (Table 2). IHC patients included in the study had normal glucose tolerance, normal body weight (Broca-index $\pm$ 10%), no history of increased alcohol consumption, and did not show hepatic cirrhosis. All had normal liver function as demonstrated by normal blood coagulation tests and normal serum albumin. Eight of the ten had slightly elevated levels of serum alanine aminotransferase (Table 2). All IHC patients were studied before starting venesection therapy. Ten healthy male subjects were studied as controls. All subjects gave informed consent. The subjects were matched for age, height, weight, and physical activity. The physical data of the IHC patients and the matched healthy controls are shown in Table 1. Mean values of age, weight, height, and physical activity were almost identical in both groups.

Table 1. Physical data and maximal insulin concentrations after an oral glucose load in patients with idiopathic haemochromatosis and matched control subjects

No.	Patients with idiopathic haemochromatosis					Matched healthy control subjects				
	Age (years)	Weight (kg)	Height (cm)	Physical activity (1–3)	Maximal insulin concentration (mU/l)	Maximal insulin concentration (mU/l)	Physical activity (1–3)	Height (cm)	Weight (kg)	Age (years)
1	22	74	182	3	60	15	3	188	75	24
2	23	74	178	1	126	50	1	186	82	21
3	36	99	192	2	180	78	2	192	95	35
4	42	80	182	1	59	30	1	193	89	45
5	48	75	178	1	103	30	1	170	69	45
6	42	86	178	1	64	38	1	186	85	43
7	48	75	180	1	136	33	2	190	89	45
8	30	70	175	2	75	58	2	169	68	32
9	39	66	168	2	90	45	2	176	60	38
10	38	72	180	2	52	32	2	182	76	39
Mean ± SD	37 ± 9	77 ± 9	179 ± 6	1.7 ± 0.7	95 ± 42	40 ± 18	1.7 ± 0.7	183 ± 9	79 ± 11	37 ± 9

Physical activity of the subjects at work and in sports was graded as 1 = low, 2 = normal, and 3 = high physical activity

Table 2. Clinical data and laboratory investigations in the patients with idiopathic haemochromatosis

No.	Serum iron (μmol/l)	Serum ferritin (ng/ml)	Transferrin saturation (%)	Serum aspartate aminotransferase (U/l)	Serum alanine aminotransferase (U/l)	Prothrombin index (%)	HLA type	Family history (no.)	Hepatic iron (0–4+)	Hepatic fibrosis (0 or +)	Iron in intestinal mucosa (0 or +)	Alcohol intake (0–3+)
1	49.0	425	88	8	10	100	A 3 B 7	3+	2–3+	0	+	0
2	39.0	599	99	10	12	100	A 3 B 7	3+	3+	0	0	1+
3	52.3	> 1000	92	32	27	100	A 3 B 2, B 37	1+	2–3+	+	+	1+
4	51.3	> 1000	90	47	42	82	A 3 BW 51	2+	3+	+	+	1+
5	40.7	1300	85	16	41	100	A 2, A 28 B 12, BW 38	1+	3+	+	ND	2+
6	40.0	538	96	28	65	88	A 3, A 10 B 7	1+	4+	+	ND	1+
7	44.3	> 1000	100	34	53	100	A 3 B 7, B 14	2+	3+	+	+	1+
8	44.9	4200	88	15	27	88	A 1, A 2 B 8, B 12	1+	3–4+	+	ND	1+
9	39.9	3530	100	15	27	95	ND	0	2–3+	+	+	1+
10	36.5	> 500	86	18	23	82	ND	2+	2+	0	ND	1+
Normal Values	< 27.0	< 300	< 50	< 17	< 23	> 80						

Family history of IHC was graded by the numbers of relatives (parents, grandparents, or siblings) with insulin-dependent diabetes, hepatic cirrhosis, or IHC. Alcohol intake was graded as 0 = no alcohol, 1 = < 20 g/day, 2 = > 20 g/day, 3 = > 60 g/day. Hepatic iron was graded according to [20]. ND = not determined

Oral glucose tolerance test

Studies were performed on recumbent subjects after an overnight fast. All had a carbohydrate intake of at least 250 g/day, abstained from alcohol for 48–72 h and were not on any drugs. An intravenous Teflon cannula was inserted in an antecubital vein. Glucose (100 g) was given orally in 400 ml water at time 0 and blood samples were taken at − 10, 0, 30, 60, 90, 120, and 180 min.

Laboratory determinations

Glucose was measured by the glucose-oxidase method [10]. Concentrations of glucagon and GIP were determined by radioimmunoassay as described previously [11–14]. The intra-assay variance for the radioimmunoassay of GIP was 6.2 ± 0.9% and the interassay variance 14.1 ± 1.2% (mean ± SEM of five assays). Commercial kits were used to measure the plasma concentrations of insulin (Pharmacia, Uppsa-

Table 3. Mean concentrations of glucose, insulin, C-peptide, GIP, and glucagon after 100 g oral glucose load in the subjects studied

		Time after 100 g glucose load (min)						
		−10	0	30	60	90	120	180
Glucose (mmol/l)	IHC patients	4.2	3.8	7.0	7.4	6.3	5.7	4.6
	Control subjects	4.3	4.3	7.2	6.9	5.7	5.3	4.3
Insulin (mU/l)	IHC patients	12	12	84[a]	72[a]	65[a]	62[a]	33[a]
	Control subjects	10	10	34	37	34	32	18
C-peptide (pmol/l)	IHC patients	0.29	0.29	0.47	0.52	0.57	0.53	0.48
	Control subjects	0.31	0.30	0.48	0.57	0.53	0.52	0.42
GIP (pg/l)	IHC patients	90	119	1017	926	910	1025	874
	Control subjects	250	247	1141	1198	981	1082	933
Glucagon (pg/l)	IHC patients	148	144	142	126	121	121	112
	Control subjects	140	141	132	124	119	115	120

[a] $p < 0.01$ between IHC patients and the matched controls

la, Sweden) and plasma concentrations of C-peptide (Novo, Copenhagen, Denmark).

Statistical methods

The statistical significance of differences between concentrations of glucose, insulin, C-peptide, glucagon, and GIP in the two groups was calculated using Wilcoxon's test for paired values.

Results

Concentrations of glucose, insulin, C-peptide, glucagon, and GIP are shown in Table 3. Insulin concentrations increased to significantly higher levels in IHC patients than in the healthy subjects ($p \leq 0.01$; Fig. 1). This difference was significant at all times between 30 and 180 min. In all 10 IHC patients, the maximal serum insulin concentration after glucose was higher when compared with the corresponding matched control subjects (Table 1). Fasting insulin concentrations were not significantly different in IHC patients compared with the healthy subjects ($p > 0.05$). Concentrations of glucose, glucagon, GIP, and C-peptide were not significantly different in IHC patients or healthy control subjects at any time ($p > 0.05$).

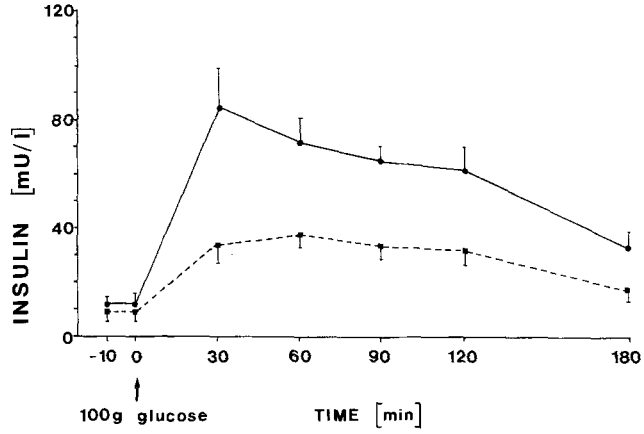

Fig. 1. Insulin concentrations of the 10 IHC patients (●——●) compared with 10 matched healthy control subjects after a 100-g glucose load (●---●). Each point represents mean ± SEM

Discussion

These results show hyperinsulinaemia after oral glucose in patients with non-cirrhotic IHC compared with healthy control subjects, even though all IHC patients had normal glucose tolerance. The association of hyperinsulinaemia and normal (or impaired) glucose tolerance is often described as insulin resistance [6–7].

Insulin resistance has been thought to occur in IHC for some time [15], since most other chronic liver diseases also show hyperinsulinaemia and insulin resistance [5–7]. There are only a few rather inconclusive studies on insulin secretion and glucose metabolism in IHC [16–17]. Two showed deficient or delayed insulin responses to oral glucose and failed to prove insulin resistance. In these studies, however, IHC patients were not characterized by liver biopsies or grouped according to their body weight, glucose tolerance or diabetes mellitus [16–17].

As iron overload in IHC may damage pancreatic α and β cells, hepatocytes and intestinal mucosa (enteroinsulinar axis), we also measured glucagon, C-peptide, and GIP. Our results show that, in the non-cirrhotic stage of the disease, β-cell function is not impaired as shown by the normal C-peptide concentrations.

In concordance with a previous study on α-cell function in IHC [18], concentrations of glucagon did not differ between IHC patients and healthy subjects. A study in diabetic IHC patients has shown that, in this stage of the disease, glucagon hypersecretion can be observed as in other types of diabetes [19]. Although iron deposits in the intestinal mucosa could be demonstrated in most non-cirrhotic IHC patients, the enteroinsulinar axis is unimpaired as shown by a normal increase of GIP after oral glucose.

Despite the difference of insulin concentrations between the IHC patients and the control subjects, absolute insulin concentrations were relatively low in both groups due to the fact that all subjects were relatively young men without impaired glucose tolerance and with relatively high levels of physical activity. Obesity, as a cause of hyperinsulinaemia and insulin resistance, was excluded by studying only subjects with normal body weight and by matching the IHC patients and the healthy subjects for body weight. Since β-cell function, glucagon secretion, and the entero-insulinar axis were demonstrated to be normal, hyperinsulinaemia and the reduced insulin effect (i.e. insulin resistance) may be related to the iron accumulation in hepatocytes. Intrahepatic shunts can be excluded because none of the subjects studied had histological evidence of cirrhosis. A receptor defect or an intracellular impairment of hepatocyte function by iron overload could also produce impaired insulin extraction. As a consequence of this, hyperinsulinaemia is achieved without insulin-hypersecretion as demonstrated by the normal C-peptide levels.

These findings and their interpretation do not rule out the possibility that, as IHC progresses, pancreatic insulin secretion may also become impaired. Indeed, this is to be expected, because of the significantly higher percentage of overt diabetes in IHC patients with cirrhosis compared to patients with cirrhosis from other causes [6]. Following-up the non-cirrhotic IHC patients in the present series may show whether the diabetic tendency of IHC is ameliorated by venesection therapy.

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