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GLUCOSE AND INSULIN METABOLISM IN PATIENTS WITH HYPERTHYROIDISM DUE TO GRAVES' DISEASE

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ABSTRACT

To clarify the impairment of carbohydrate metabolism in hyperthyroidism, we performed the oral glucose tolerance test (OGTT) and glucagon tolerance test in ten patients with hyperthyroidism due to Graves' disease (GD) and in ten normal subjects. During OGTT, glucose and insulin values in the GD patients were twice as high as those in the normals. The ratio of cumulative net plasma glucose [ΣPG (0−120 minutes)] and insulin [ΣIRI (0−120 minutes)] was 0.83±0.14 and 1.14±0.25 in the GD patients and normals, respectively.

During the glucagon tolerance test, plasma glucose showed lower peaks in the GD patients than in the normals. C-peptide reached a peak value at 6 min in the GD patients and at 10 min in the normals. Cyclic AMP response in the GD patients was three times greater than that in the normals.

A smaller insulinogenic index and a smaller ΣPG/ΣIRI ratio in the GD patients suggest that the secretion of insulin in GD patients does not meet the demand despite the higher insulin values observed during OGTT. Greater response of cAMP, smaller and earlier peaks of C-peptide and smaller response of glucose to glucagon in the GD patients may suggest a rapid insulin turnover and a reduction of glycogen storage in the liver with hyperthyroidism.

Key Words: Glucagon, Insulin, Glucose, Graves' Disease

Abnormal glucose tolerance is often observed in patients with hyperthyroidism.[1−3] Fifty-seven percent of patients with hyperthyroidism have also been reported to be diabetic according to Kreines et al.[1] Several possibilities have been reported to explain this finding: an enhanced gastric emptying,[4] an increased intestinal absorption rate,[5−7] an augmented production of endogenous glucose,[8, 9] a change in metabolic clearance rate of insulin[10] and peripheral resistance to the action of insulin.[11, 12] To clarify the mechanisms involved, we examined the response of blood glucose and insulin during the oral glucose tolerance test (OGTT) and the response of blood glucose, serum C-peptide and plasma cyclic AMP during the glucagon tolerance test in patients with hyperthyroidism vs. normal subjects matched for age and sex. In addition, to clarify the role of the liver in hyperthyroidism, the glucagon tolerance test was also performed in patients with liver cirrhosis.

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SUBJECTS, MATERIALS AND METHODS

Subjects

A total of ten untreated patients with Graves' disease, two men and eight women ranging in age from 16 to 26 years, and 13 patients with liver cirrhosis, nine men and four women ranging in age from 46 to 72 years participated in the study (Table 1). The diagnosis of Graves' disease was established from the typical symptoms, thyroid function test abnormalities, presence of TSH-binding inhibitory immunoglobulin, and an increased ^{123}I-uptake of the thyroid. The diagnosis of liver cirrhosis was based on blood chemical examination, echogram and indocyanine-green infusion test (ICG) results. Patients having an ICG value of more than 15% were recruited for this study. Ten normal volunteers, two men and eight women, ranging from 19 to 26 years served as the control group.

Table 1. Profiles of the Subjects

	n	Age years	HbA1c %	T_3 nmol/l	T_4 nmol/l	TSH μU/ml
Normal	10	21.4±0.7	4.9±0.1	2.43±0.03	159.3±5.2	1.10±0.14
Graves'	10	20.2±1.3	5.0±0.3	10.26±0.26	278.0±18.0	———
Liver Cirrhosis	13	59.5±2.0	———	———	———	———

Results are mean±SE.

Methods

At 0800, following an overnight fast, each subject received a dose of 75g of glucose in 225ml of water while resting in bed. Blood samples were withdrawn from the antecubital vein at 0, 30, 60, 90 and 120 min after ingestion. At least five days after this glucose tolerance test, the glucagon tolerance test was performed. At 0800, an indwelling needle was placed in an antecubital vein and 1mg of glucagon (Novo-Nordisk, Kopenhagen, Denmark) was injected intravenously as a bolus. Blood was drawn at 0, 3, 6, 10, 30 and 60 min. Samples intended for assay of cyclic AMP were transferred immediately into chilled polypropylene tubes containing 120ml of EDTA-4Na and stored at −20°C until assay.

Assays

Commercially available immunoassay kits were used to measure the serum concentrations of C-peptide (C-peptide RIA Shionogi, Shionogi, Japan), TSH (IMX TSH Dinapack Kit, Dinabot Japan, Japan), T_3 (IMX T_3 Dinapack, Dinabot Japan, Japan), T_4 (IMX T_4 Dinapack, Dinabot Japan, Japan) and cyclic AMP (cyclic AMP assay Kit, Yamasa, Japan). The concentration of blood glucose was measured by the glucose oxidase method.

Statistical evaluation

All data were expressed as mean±SE. Statistical evaluation was performed using Sheffe's multiple comparison, with $P < 0.05$ accepted as statistically significant.

RESULTS

Response of plasma glucose and insulin during OGTT

Six of the ten patients with Graves' disease showed an impaired glucose tolerance according to WHO criteria and none were diabetic. The basal glucose value was 5.23±0.11 mmol/l in the GD patients vs. 4.87±0.07 mmol/l in the normal subjects. In the GD patient group, plasma glucose reached a peak of 9.97±0.42mmol/l at 30 min ($P < 0.001$ compared with normal group), and declined to 8.01±0.71 mmol/l at 120 min. In the normal subjects, plasma glucose reached a peak of 5.73±0.36 mmol/l at 30 min, declined to 4.21±0.25 mmol/l at 60 min and then reached a plateau (Fig. 1.).

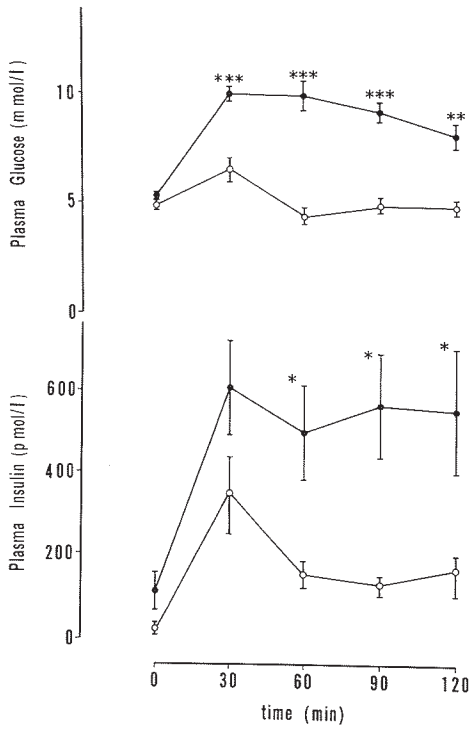

Fig. 1. Response of plasma glucose and insulin during OGTT in patients with Graves' disease and in normal subjects

●—● Graves' disease, ○—○ Normal subjects

Values of plasma glucose (upper panel) and IRI (lower panel) during 75g OGTT are shown with mean±SE in the patients with hyperthyroidism and in the normal subjects. *$p < 0.05$, **$p < 0.01$, ***$p < 0.001$ compared with normal subjects.

Basal insulin values were 115.2±57.0 pmol/l in the GD patients and 28.2±6.6 pmol/l in the control group. In the GD patient group, insulin reached a peak of 605.4±123.0 pmol/l at 30 min, declined to 492.6±126.6 pmol/l at 60 min, then reached a plateau. In the normal subjects, insulin peaked at 351.6±90.6 pmol/l at 30 min, declined to 140.4±36.0 at 60 min and reached

a plateau (Fig. 1). Values at 60, 90 and 120 min in the GD patients were significantly higher than those in the control subjects.

To determine whether insulin secretion is sufficient to control blood glucose, several indices were estimated: The insulinogenic index was 1.1 in the GD patients vs. 2.9 in the normal subjects. The ratio of ΣPG (0−120 min) and ΣIRI (0−120 min) was 0.83±0.14 and 1.14±0.25 in the GD patients and the normal subjects, respectively. The difference between plasma glucose values at 30 and 60 min, ΔPG (30−60 min) and that between insulin values at 30 and 60 min ΔIRI (30−60 min) were calculated. The ratio of ΔPG/ΔIRI (30−60) was −0.12±0.20 and 0.64±0.29 in the GD patients and normals, respectively.

Plasma glucose and C-peptide response to glucagon

Basal values for plasma glucose were 4.89±0.13 and 4.85±0.12 mmol/l in the GD patients and the normal subjects, respectively. In the GD patients, the plasma glucose peaked at 6.12±0.36 mmol/l at 30 min, declining to 4.87±0.14 at 60 min. In the normal subjects, the plasma glucose reached a peak of 6.88±0.32 mmol/l at 30 min, declining to 4.37±0.22 at 60 min (Fig. 2).

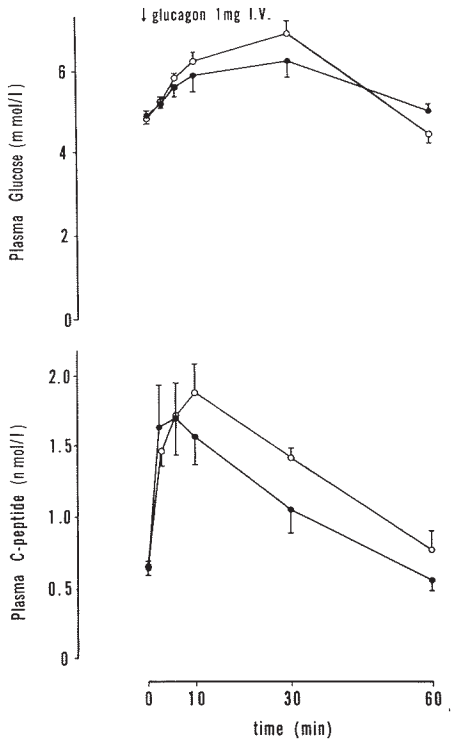

Fig. 2. Response of plasma glucose and C-peptide to glucagon in patients with Graves' disease, and in normal subjects

●—● Graves' disease, ○—○ Normal subjects

Values of plasma glucose (upper panel) and c-peptide (lower panel) are shown with mean±SE before and after intravenous injection of 1mg of glucagon in the patients with hyperthyroidism and in the normal subjects.

Basal C-peptide values were 0.59±0.08nmol/l in the GD patients and 0.62±0.07 in the normal subjects. The peak achieved in the GD patients was 1.71±0.21 at 6 min, while the peak in the normal subjects was 1.80±0.24 nmol/l at 10 min. The C-peptide value declined to 0.55±0.08 in the GD patients and to 0.76±0.07 in the normal group. The differences in the values between the GD patients and the normal subjects at each time were not statistically significant (Fig. 2).

In the patients with liver cirrhosis, the basal plasma glucose value was 10.43±1.36 mmol/l ($P < 0.001$ compared with normals), exhibiting a peak of 11.80±1.32 mmol/l ($P < 0.001$ compared with normals) at 30 min and declined slightly to 11.65±0.81 at 60 min. The C-peptide value rose from an initial value of 0.83±0.09 nmol/l, achieving a peak of 1.46±0.22 at 3 min and declining to 0.80±0.09 at 60 min (Table 2).

Table 2. Responses of Plasma glucose and C-peptide to Glucagon in Patients with Liver Cirrhosis

Time	0	3	6	10	30	60'
Plasma glucose	10.43	10.23	10.51	10.84	11.80	11.65
(mmol/l)	±1.36	±1.31	±1.35	±1.34	±1.32	±0.81
C-peptide	0.83	1.46	1.43	1.30	0.92	0.80
(nmol/l)	±0.09	±0.22	±0.17	±0.14	±0.07	±0.09

Plasma glucose and C-peptide concentrations were determined in 13 patients with liver cirrhosis. Results are mean±SE.

Cyclic AMP response to glucagon (Table 3)

The basal values of cyclic AMP were 18.0±2.8, 15.8±0.9, and 15.2±0.5 pmol/ml in the patients with hyperthyroidism, the patients with liver cirrhosis, and the normal subjects, respectively. At 10 min the values increased to 911.0±66.1, 303.9±41.7, and 411.0±56.1 pmol/ml, respectively. The difference between the normal subjects and the hyperthyroidism patients was statistically significant ($p < 0.001$). The difference in the values between the normal subjects and the patients with liver cirrhosis was also significant ($p < 0.001$).

Table 3. Cyclic AMP Response to Glucagon

	Cyclic AMP (pmol/ml)	
Minutes	0	10
Normal	15.2±0.5	411±56.1
Graves'	18.0±2.8	911.0±66.1***
Liver Cirrhosis	15.8±0.9	303.9±41.7***

Plasma cyclic AMP concentrations were determined before and 10 min after intravenous injection of lmg of glucagon. Results are mean±SE. *** $p < 0.001$ compared with normal subjects.

DISCUSSION

Data obtained in rats, sheep, and humans suggests that thyroid hormone accelerates insulin degradation.[10,13,14] In our study, the peak values for C-peptide appeared at 6 min in the hyperthyroid patients and at 10 min in the control group during the glucagon tolerance test. In addition, the C-peptide value at 60 min was lower in the hyperthyroid patients compared with the normal subjects, suggesting that the secretion of insulin is exaggerated and the degradation of insulin is accelerated in this disease, although the change of insulin/C-peptide ratio is still under discussion.[15] An accelerated insulin turnover may also explain the higher plasma glucose value at 60 min in the patients with hyperthyroidism as compared with the normal subjects. In this study, C-peptide was estimated instead of insulin concentration because of the possible existence of anti-insulin antibody in the patients with autoimmune thyroid disease. For a more accurate conclusion, both insulin and C-peptide concetrations should be determined at the same time.

The intravenous administration of glucagon activates the adenylate cyclase system, increases cyclic AMP, initiates both glycogenolysis and gluconeogenesis, and leads to a rise in blood glucose.[16–19] Thyroid hormone is also known to activate the adenylate cyclase system,[20,21] with additional evidence accumulating, i.e., an increase in cyclic AMP generation in the myocardium of cats,[22] in the adipose tissue of rats,[23,24] and in human plasma.[25,26] In this study, the response of cyclic AMP to glucagon was significantly higher in the hyperthyroid patients than in the normal subjects, consistent with previous reports.[26,27] However, the response of plasma glucose to glucagon was smaller in the patients with hyperthyroidsm than in the normal subjects. The discrepancy between a high response of cyclic AMP and a small response of plasma glucose may be explained by a decrease in glycogen storage in the liver in hyperthyroidism.[28–30] A significantly smaller response of cyclic AMP and plasma glucose in the patients with liver cirrhosis as compared with that in the normal subjects may support this theory. And this may be due to the fact that increased plasma glucose induced by an injection of glucagon mostly emanates from the liver,[18,31] and that the hepatocytes are destroyed and/or lacking in glycogen in liver cirrhosis.[32,33]

A rapid absorption of carbohydrates has been proposed to explain the abnormality of glucose metabolism in hyperthyroidism.[5–7] In addition, insulin resistence in the peripheral tissues, which has been observed in hyperinsulinemia associated with hyperglycemia, might exaggerate hyperglycemia in patients with Graves' disease.[34,35] However, these explanations cannot fully describe the abnormality. Only two patients in our study showed oxyhyperglycemia. Another six showed an impaired glucose tolerance, while two remained within the normal range. The smaller insulinogenic index of the hyperthyroid patients may suggest shortness of a supply of insulin inadequate to overcome the rapid increase in blood glucose. A smaller ΔPG (30–60 min)/ΔIRI (30–60 min) in the GD patient group may also suggest a shortness of insulin 30 min after glucose intake. In addition, the smaller ΣPG (0–120)/ΣIRI (0–120) in the GD patient group may indicate an inability to meet the demand for insulin in hyperthyroidism.

Thus, our study showed a smaller response of glucose during the glucagon tolerance test and an inadequate level of insulin despite twice the value of insulin observed during OGTT in the hyperthyroid patients as compared with the normal subjects. An explanation for these results may be a quick turnover of insulin in patients with hyperthyroidism due to Graves' disease.

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