CARBOHYDRATE METABOLIC DISTURBANCES IN HYPERTHYROIDISM

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ABSTRACT

Twenty five hyperthyroid patients and 25 healthy volunteers were evaluated for carbohydrate metabolic disturbance with an oral glucose tolerance test and glycosylated haemoglobin percentage. Insulin secretory response was studied in 17 hyperthyroids and 10 controls. A varying degree of abnormality was noted in hyperthyroids. Forty per cent patients had a significantly higher glycosylated haemoglobin and 3 (12%) patients had impaired glucose tolerance and 1 (4%) patient had frank diabetes mellitus. Significant hyperinsulinism was seen in the hyperthyroid group. Our data suggests that carbohydrate metabolic aberration exists in hyperthyroids and may reflect insulin resistance.

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KEY WORDS : Carbohydrate metabolism; Hyperthyroidism; Insulin resistance.

Introduction

Many hormones such as catecholamines, glucagon, cortisol, and thyroxine, either singly or through their influence on each other, affect carbohydrate metabolism so as to elevate blood sugar levels [1]. However, conflicting levels of glycaemia have been seen in hyperthyroidism. The status of insulin secretion and its responsiveness, though reported to be affected, in hyperthyroids has not been emphasized [1]. We undertook the present study to assess the glycaemic state and to study the insulin secretory response in these patients.

Material and Methods

We studied 25 patients with hyperthyroidism and compared their results with 25 healthy matched controls. Patients with history of diabetes mellitus or known to be taking drugs like thiazides, anticonvulsants, beta blockers, and steroids that were likely to affect carbohydrate metabolism were excluded from the study [2]. Patients were screened for anaemia which was likely to give false low levels of glycosylated haemoglobin. The diagnosis of hyperthyroidism was confirmed by ra-

dioactive I¹³¹ uptake studies, raised thyroxine (T4) and/or triiodothyronine (T3) levels.

All patients and controls were evaluated for carbohydrate disturbances by an oral glucose tolerance test (OGTT) and glycosylated haemoglobin percentage (GHB%). OGTT was carried out as per World Health Organization recommendations [2] after the subjects had been placed on a standard diet containing 250 g of carbohydrate for 3 days.

GHB% was estimated by the ion exchange resin method (Stagnen Immunodiagnostic Ltd). The method is based on the property of unglycosylated haemoglobin binding to a weak cation exchange resin leaving glycosylated haemoglobin in the supernatant. GHB% was estimated by measuring the absorbance of GHB fraction and that of total haemoglobin at 415 nm wave length [2]. Insulin levels were measured by radioimmunoassay (BARC-Kits) during OGTT at 0, 30, 60 and 120 minutes.

Results

In the hyperthyroid group the mean age of patients was 36.12 ± 10.4 years (range 20-61 yrs); there were 14 males and 11 females. Twenty two

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(88%) patients had a goitre. It was diffuse in 18 (72%), multinodular in 3 (12%), and there was a solitary nodule in 1 (4%) patient.

Primary hyperthyroidism was confirmed by a high radioactive I^{131} uptake values at 2, 4, 6, 24 and 48 hours with or without the presence of increased hepatic counts. Mean uptake values in patients are shown in Table 1. The mean serum values of T3 was 4.5 ± 2.5 ng/mL, and that of T4 was 16.9 ± 3.1 μ g/mL in patients with hyperthyroidism. All cases had low TSH levels implying a primary hyperthyroid state. Further analysis of thyroid hormone levels showed that 5 (20%) patients suffered from T3 toxicosis, 7 (28%) suffered from T4 toxicosis and 13 (52%) had combined T3+T4 toxicosis (Table 2).

TABLE 1

Radioactive I^{131} thyroid uptake values and hepatic counts in patients

Values	2h	4h	6h	24h	48h
I^{131} thyroid uptake (% dose administered)					
Mean $\pm$ SD	32.9 26.7	49.6 28.1	56.2 19.8	50.9 20.4	42.5 19.1
Hepatic count/minute					
Mean $\pm$ SD	— —	— —	— —	241 118	278 142

TABLE 2

Thyroid hormone assays in patients

Group	No of cases	Value of thyroid hormone Mean $\pm$ SD	
		T3 ng/mL	T4 μ g/mL
T3 Toxicosis	5	6.06 ± 1.91	12.01 ± 1.82
T4 Toxicosis	7	1.60 ± 0.4	17.93 ± 2.32
T3 + T4 Toxicosis	13	5.78 ± 2.13	18.65 ± 1.53
Total	25	4.52 ± 2.51	16.92 ± 3.08

Cytological studies in all cases showed thin colloid admixed with cells, some of which had the fire-flare appearance. This confirmed the diagnosis of hyperthyroidism and ruled out thyroiditis. Frank diabetes mellitus was seen in 1 patient and impaired glucose tolerance in 3 (12%) patients.

The mean fasting blood sugar levels were comparable in the hyperthyroid patients and normal

controls. However a significant increase in blood glucose levels (at 30, 60 and 120 minutes) and GHB% was noted in hyperthyroid patients (Table 3). Within the hyperthyroid group no difference was noted in the blood sugar levels between the T3, T4, and T3+T4 toxicosis group (Table 4).

TABLE 3

Effect of hyperthyroidism on OGTT & GHB%

	Hyperthyroid (n=25) Mean $\pm$ SD	Control (n=25) Mean $\pm$ SD
Blood glucose (mg/dL)		
Fasting	81.3 ± 21.6	77.3 ± 8.1
30 minutes	139.9 ± 36.7	110 ± 13.3
60 minutes	132.7 ± 45.6	98.2 ± 12.3
120 minutes	99 ± 25.3	79.9 ± 8.22
GHB%	11.7 ± 3.98	7.63 ± 1.99

OGTT - Oral glucose tolerance test; GHB% - Glycosylated haemoglobin percentage

In the control group a positive correlation was seen between the plasma glucose levels and plasma insulin ($r = 0.77$) while no such correlation could be demonstrated amongst the hyperthyroid patients. The plasma insulin levels in the latter group remained elevated throughout the OGTT period even after the plasma glucose returned to normal (Table 5).

Discussion

The effect of hyperthyroidism on carbohydrate metabolism has been reported differently in various studies [3,4]. While some have demonstrated a hyperglycaemic response others have failed to show any significant abnormalities. In our study varying degrees of hyperglycaemia was noted in 16 per cent of the hyperthyroids. However, when GHB% was used as a yardstick the abnormal responses were seen in 40 per cent patients. This indicates that GHB%, which is a measure of time-averaged glycaemic control, is a more sensitive index of overall carbohydrate metabolic disturbance.

We found no correlation between the severity of hyperthyroidism and plasma glucose levels, nor could we demonstrate any significant inter-group differences between T3, T4, or T3+T4 toxicosis group. This was consistent with the observations published in earlier studies [3,5]. Our sample population was not large enough to draw any con-

TABLE 4

Effect of T3, T4, and T3 + T4 toxicosis on OGTT and glycosylated haemoglobin %

Parameter	T3 Toxicosis	T4 Toxicosis	T3 + T4 Toxicosis
Plasma glucose mg/dL			
Mean $\pm$ SD			
Fasting	77 $\pm$ 8.9	77.4 $\pm$ 12.5	85 $\pm$ 28.9
30 minutes	139.6 $\pm$ 33.7	138.9 $\pm$ 40.9	138.2 $\pm$ 40.1
60 minutes	123.8 $\pm$ 30.1	114.6 $\pm$ 47.1	145.8 $\pm$ 50.2
120 minutes	95.4 $\pm$ 16.7	96.1 $\pm$ 35.0	101.5 $\pm$ 25.8
Glycosylated hemoglobin%	11.1 $\pm$ 5.1	11.8 $\pm$ 5.1	11.4 $\pm$ 4.1

TABLE 5

Insulin kinetics in response to oral glucose tolerance test

Parameters	Hyperthyroid n=17		Control n=10	
	Plasma glucose mg/dL Mean $\pm$ SD	Insulin microunits/mL Mean $\pm$ SD	Plasma glucose mg/dL Mean $\pm$ SD	Insulin microunits/mL Mean $\pm$ SD
Fasting	93.4 $\pm$ 25.3	19.5 $\pm$ 11.8	75.4 $\pm$ 4.7	8.4 $\pm$ 3.4
30 mts	133.5 $\pm$ 40.4	61.8 $\pm$ 44.7	112.8 $\pm$ 8.8	22.1 $\pm$ 10.7
60 mts	133.7 $\pm$ 55.5	70.8 $\pm$ 50.6	100.8 $\pm$ 6.1	20.4 $\pm$ 7.9
120 mts	95 $\pm$ 25.5	70.9 $\pm$ 61.2	81.4 $\pm$ 4.6	16.1 $\pm$ 9

clusions on the effect of age or type of thyroid diseases on carbohydrate tolerance. However, Kreines et al [3] have reported carbohydrate intolerance to be more common in older patients with toxic nodular goitre than in the younger patients with Graves' disease.

The etiology of carbohydrate intolerance in hyperthyroidism is multi-factorial and the metabolic abnormality occurs at multiple sites. The occurrence of significantly higher peak plasma glucose levels at 30 minutes and 60 minutes in our hyperthyroid patients suggests that increased rates of gastric emptying and intestinal absorption may have a role in the genesis of this defect [6,7].

The augmented glucose production in these patients has also been attributed to many factors like increased uptake of gluconeogenic precursors [8,9], a direct effect of thyroid hormones [9-12], hypersecretion of glucagon [5,13] and altered sensitivity to catecholamines [14]. Moreover, in experimental models of hyperthyroidism, an increased activity of gluconeogenic enzymes like glucose-6-phosphatase and phosphoenol pyruvate

carboxykinase, and cyclic AMP have also been demonstrated [11,15]. Hyperinsulinism has been a consistent finding by many workers [5,6,16,17] and we found it to persist at even 2 hours of OGTT. This phenomenon has been attributed to increase beta cell mass [16], decreased hepatic extraction of insulin [18], excessive secretion of pro-insulin [19], and probably as a response to hyperglycaemia itself [12].

Several workers have reported a state of insulin resistance in hyperthyroidism [5,20,21]. In our study too we noted hyperinsulinemia. However, without estimation of pro-insulin levels, which forms a portion of insulin hypersecretion but binds poorly to insulin receptors, we were not able to comment with certainty on insulin resistance. Similarly no inference could be drawn on the rate of insulin degradation, which requires the study of C-peptide/insulin molar ratios.

Despite the complex and incompletely understood infractions of these various factors our study has shown that a significant number of patients with hyperthyroidism have hyperglycaemia with

increased levels of immunoreactive insulin. The former can be better documented by measuring GHb% rather than OGTT.

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