THYROID HORMONES IN NON-INSULIN-DEPENDENT DIABETES BEFORE AND AFTER THERAPY

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ABSTRACT

Twenty patients of non-insulin-dependent diabetes mellitus (NIDDM) (15 males and 5 females) who developed secondary failure to oral hypoglycaemic drugs, were evaluated for thyroid hormone abnormalities before and after control of diabetic state with insulin. Blood glucose (mean $\pm$ SEM mg/dL) fasting and post prandial levels were 260 ± 16 and 370 ± 20 respectively before therapy. After 15 days of intensive insulin therapy these levels fell to 110 ± 14 and 130 ± 12 respectively ($p < 0.005$). Glycosylated haemoglobin percent (GHb%) (mean $\pm$ SEM) was 10 ± 0.4 before therapy and after therapy it fell to 9.2 ± 0.3 ($p < 0.05$). Serum tri-iodothyronine levels (mean $\pm$ SEM ng/mL) were 0.55 ± 0.03 which was significantly lower ($p < 0.05$) as compared controls. After therapy it significantly ($p < 0.05$) rose to 1.22 ± 0.08 . Serum thyroxine (T4) (mean $\pm$ SEM mcg/dL) was 8.5 ± 0.6 before therapy and it did not change significantly after therapy. Serum reverse tri-iodothyronine (rT3) values of (mean $\pm$ SEM ng/dl) 0.24 ± 0.05 were higher before therapy and decreased to 0.20 ± 0.02 after therapy. However thyrotropin (TSH) values before and after therapy remained same. There was no significant change in TSH response to thyrotropin releasing hormone (TRH) before and after control of diabetic state.

It was concluded that peripheral changes in T3, T4 and rT3 (low T3, high rT3 and low or normal T4) occurred in uncontrolled diabetic state. However, pituitary thyrotroph function in NIDDM with ideal body weight was not significantly affected.

MJAFI 1995; 51 : 117-121

KEY WORDS : Thyroid hormones; Non-insulin-dependent diabetes mellitus.

Introduction

In a normal healthy individual, the thyroid gland secretes whole of circulating thyroxine (T4), less than 25% of triiodothyronine (T3) and about 3% of circulating reverse triiodothyronine (rT3). T4 serves as the main prohormone for the metabolically and biologically more active T3. This conversion of T4 into T3 occurs in the peripheral tissue by 5' monodeiodination [1]. Some circulating T4 is converted to rT3 by 5 deiodinase. This rT3 is present in very low concentration in healthy persons and is metabolically inert.

The association between the levels of carbohydrate intake and T3 production from T4 was first demonstrated by Danforth and col-

leagues in animals [2]. Subsequently several laboratories showed that the inclusion of carbohydrates in hypocaloric diets is essential for normal serum T3 levels in human subjects [3,4]. Others reported that glucose enhances T3 production in rat-liver homogenates enriched with T4 in vitro [5,6]. However study of thyroid hormone abnormalities in deranged carbohydrate metabolism are rather few in human beings.

We have earlier reported thyroid function abnormalities in acute illness like diabetes ketoacidosis [7]. Thyroid function in non-insulin-dependent diabetes mellitus (NIDDM) are poorly documented and moreover data concerning pituitary thyrotroph function in NIDDM are very limited. The basal and TRH stimulated TSH secretion have

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not been studied in patients of NIDDM before and after therapy with attainment of optimum metabolic control. The present study was therefore planned to evaluate thyroid functions in NIDDM.

Material and Methods

Twenty patients of NIDDM (15 males and 5 females with ages ranging from 45-60 years) who developed secondary failure to oral hypoglycaemic drugs were included in the present protocol. None of these patients had received insulin earlier. The patients continued to be hyperglycaemic (fasting sugar more than 200 mg/dL) despite maximum dietary effort and maximum doses of oral hypoglycaemic agents (OHA). All these patients had weakness, easy fatiguability and various other symptoms of uncontrolled diabetes mellitus. None of them had any evidence of hepatic or renal disease or ketonuria on routine screening. All patients were clinically euthyroid and were within 10% of their body weight documented by BMI.

All patients were admitted to achieve better metabolic control with insulin therapy. They were placed on standardised diets varying from 1500 to 1800 calories per day. After an overnight fast, a catheter was inserted in the antecubital vein and blood samples for glucose, T3, T4, rT3, TSH, and glycosylated hemoglobin (GHb) were taken. TRH stimulation test was carried out in 10 patients by giving a bolus of 200 µgm of TRH (Hoechst) and blood samples for TSH were collected at 0, 20, 40, 60 and 90 minutes. The diabetes was fully controlled within 15 days of insulin therapy (fasting blood sugar 120 mg/dL & post-prandial 140 mg/dL). This control was maintained for 6-8 weeks before repeating the thyroid function tests and GHb estimation.

Ten, age and sex matched controls were also studied for blood glucose, T3, T4, rT3, TSH and GHb% level. TRH stimulation was carried out in 5 controls. Blood samples for thyroid hormones were stored at -20°C for subsequent assays.

Estimation of Blood Glucose : Blood glucose estimation was done by Technicon

Auto-analyser II system based on reaction of a cupric neocuproine chelate with glucose. This method is specific for glucose and has a high degree of precision and reproducibility.

Thyroid Hormone Assay : The estimation of T3 and T4 was done by RIA kits (RIAK/4 & 5) supplied by Bhabha Atomic Research Centre (BARC). Estimation of rT3 was done by RIA kit supplied by Amersham. TSH estimation was done by TSH-IRMA kit 9 supplied by BARC. The inter- and intra-assay coefficient of variation in all assays was less than 8%.

Estimation of Glycosylated Haemoglobin: This was done by ion exchange resin method with kits supplied by Stangen Immunodiagnosics.

Results

Blood Glucose and GHb% Values : Blood glucose and GHb% values in patients and controls are given in Table 1. It shows that fasting and post-prandial blood glucose levels before therapy were (mean $\pm$ SEM) 260 $\pm$ 16 mg/dL and 370 $\pm$ 20 mg/dL respectively. After 15 days of intensive insulin therapy fasting blood glucose came down to 110 $\pm$ 14 mg/dL and post-prandial blood glucose fell down to 130 $\pm$ 12 mg/dL ($p < 0.005$). GHb% before therapy was 10 $\pm$ 0.4 and after insulin therapy it fell down to 9.2 $\pm$ 0.3 ($p < 0.05$).

TABLE 1
Glucose and GHb% values in patients and controls

	Before insulin therapy (n=20)		After insulin therapy (n=20)		Control (n=10)	
	F	PP	F	PP	F	PP
Blood glucose (mean $\pm$ SEM, $\pm$ 16 $\pm$ 20 mg/dL)	260	370	110**	130**	77.30	90
GHb% (mean $\pm$ SEM)	10.2		9.2*		6.8	
	$\pm$ 0.4		$\pm$ 0.3		$\pm$ 0.2	

* $p < 0.05$ versus before insulin therapy

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Thyroid Hormone Values : Table 2 shows thyroid hormone values in patients before and after 6-8 weeks insulin therapy. T3

concentration before therapy (0.53 ± 0.03 ng/dL) was significantly lower as compared to controls. After therapy T3 values rose significantly well within the euthyroid range as compared to control. Serum T4 did not change significantly after therapy.

TABLE 2
Thyroid hormones in patients and controls

Serum hormones	Before therapy (n=20)	After insulin therapy (n=20)	Control (n=10)
T3 (ng/mL)	0.53 ± 0.03	1.22* ± 0.08	0.7 - 2.0
T4 (μ g/dL)	8.5 ± 0.6	9.8 ± 0.4	5.4 - 13.5
rT3 (ng/mL)	0.24 ± 0.05	0.20 ± 0.02	0.04 - 0.4
TSH (μ U/mL)	1.9 ± 0.4	3.2 ± 0.4	0.2 - 5.1

(* $p < 0.05$ versus before therapy)

In contrast serum rT3 value was higher in diabetics before therapy and it decreased after insulin. However the values of rT3 before and after therapy remained within the normal range. TSH values before and after therapy did not change and were within normal range.

TRH Stimulation Test : The TSH response to TRH studied in 10 patients is given in Table 3. It showed that there was no significant change in TSH response to TRH before and after therapy with insulin.

Discussion

Recent studies demonstrate that much of T3 found in the blood of normal man arises not by direct secretion from thyroid gland but rather from peripheral monodeiodination of T4 in its outer ring at the 5' position [1]. Thus T4 serves as the main prohormone for T3. On the contrary, rT3 is metabolically inert. It is well documented that serum levels of T3, T4 and rT3 may be altered in patients with chronic illnesses like malnutrition, anorexia nervosa, renal disorders or prolonged febrile illness. These patients may have low T3, elevated rT3 and normal or low normal levels of

TABLE 3
TRH stimulation tests in patients and controls (TSH values mean $\pm$ SEM μ u/mL)

Time (min)	Before therapy (n=10)	After therapy (n=10)	Control (n=5)
0	0.1 ± 0.04	0.2* ± 0.02	1.8 ± 0.02
20	2.0 ± 0.2	2.66* ± 0.06	2.8 ± 0.2
40	2.4 ± 0.08	4.15* ± 0.08	5.8 ± 0.2
60	2.8 ± 0.06	3.33* ± 0.02	4.6 ± 0.1
90	1.96 ± 0.08	2.15* ± 0.02	2.8 ± 10.2

(* $p > 0.05$ versus before therapy)

T4. Their biochemical findings are indicative of euthyroid sick syndrome and does not reflect any primary thyroid dysfunction. This low T3 syndrome is representative of adaptive mechanism for energy conservation during periods of prolonged catabolism. The metabolically active T4 is converted into inert rT3 rather more active T3. Thyroid function abnormalities in IDDM with diabetic ketoacidosis have been reported by various workers [7-10]. Gilani et al [8] reported significantly higher basal TSH with either normal or low T4 and normal or elevated rT3 in IDDM cases. They stressed that elevated TSH with low rT3 is indicative of primary hypothyroidism in patients with non-thyroidal illness.

In the present study, we have evaluated thyroid functions in NIDDM cases who were not obese and presented with symptoms of uncontrolled diabetes mellitus even with maximum dosage of OHA. None of them had evidence of ketoacidosis at presentation. They were treated intensively with insulin for 15 days to bring down blood sugar and control was maintained for 6-8 weeks before thyroid functions were re-evaluated.

Serum T3 was initially significantly ($p < 0.05$) lower as compared to controls (0.53 ± 0.03 vs $0.7 - 2.0$) and with control of hyperglycaemia it came to normal range. The circulating T4 (8.5 ± 0.6 mcg/dL) was well within euthyroid range and after therapy it did not

change significantly. rT3 (0.24 ± 0.05 ng/mL) was high before therapy and it decreased after control of hyperglycaemia however the values remained in the normal range. TSH value remained unchanged before and after therapy. Alexander et al [11] also noticed mild persistent depression of T3 and elevation of rT3 which resolved partially with insulin therapy.

The changes in thyroid hormones in untreated obese NIDDM have been attributed by Sheppard et al to insulin resistance at cellular level [12]. These changes of thyroid hormones reverted to normal with control of diet and reduction of weight. However, in our study this factor did not appear to have played a role since the patients were of ideal body weight. Therefore, it appears that hyperglycaemia per se is responsible for aberration in thyroid functions as none of the patients had ketacidosis on admission.

The caloric intake has been shown to modulate the T3 production from T4 in healthy men undergoing fasting, as well as in liver preparations of fed and fasting animals [5,6]. Carbohydrate content of the diet particularly appears to influence the T3 production from T4 [3,4]. Reduced T3 production induced by fasting has been explained by changes in concentration of deiodinating enzyme [13,14] and changes in concentration of reduced glutathione [14,15]. An alternative explanation offered by others is that during caloric deprivation transport of T4 and T3 into tissue is diminished and this phenomenon is more pronounced for T4 than T3. It is postulated that irrespective of any possible change in 5'-deiodinase activity, inhibition of T4 transport per se may contribute to low T3 production and low T3 serum levels due to reduced substrate (i.e. T4) permeability in tissues. Therefore, suppressed T3 production in our diabetic patients, a situation where tissues are deprived of calories inspite of persistent hyperglycaemia, is understandable.

Reports regarding TSH status in NIDDM are conflicting. Sheppard et al [12], and Kabadi et al [16] reported reduced T3 and

increased rT3 in obese NIDDM patients. Since TSH concentration was reduced, hypothalamic-pituitary dysfunction in NIDDM was considered as the cause for aberration in thyroid hormones. Diminished TSH response to TRH, due to lack of glucose entry into thyrotroph cells, though considered, may not be the only causative factor since previous studies reported that prompt attainment of euglycaemia by insulin therapy did not normalise the TSH secretion [17,18].

In our patients and controls the TSH response to TRH was relatively low as compared to results obtained by other studies [17,19]. The reason for this is not clear. It may be due to difference in control of diabetic state. However, some others [19,20] like us, have also reported normal pituitary function in NIDDM.

It appears therefore that peripheral hormonal changes in T4, T3 and rT3 levels in NIDDM cases are like IDDM cases though less marked in degree. However, pituitary thyrotroph function, in NIDDM with normal body weight, remains unaffected as against thyrotroph dysfunctions noted in IDDM. This may be due to the fact that acute insulinopenia in IDDM leads to inadequate insulinization of ventromedial hypothalamus leading to alteration in TRH secretion in this subset of diabetics. Physicians should therefore keep these changes in mind before evaluating diabetics for thyroid hormone dysfunctions.

REFERENCES

1. Ingbar SH, Braverman LE. Active form of the thyroid hormones. *Ann Rev Med* 1975; 26 : 443-5.
2. Danforth Jr E, Sims EAH, Horton ES, Goldman RF. Correlation of serum triiodothyronine concentration with dietary composition, gain in weight and thermogenesis in man [abstract]. *Diabetes* 1975; 24 : 406a.
3. Splanding SE, IJ Copora, RS Sherwin, SS Lyall. Effects of caloric restriction and dietary composition on serum T3 and reverse T3 in man. *J Clin Endocrinol Metab* 1976; 42 : 197-9.
4. Harris ARC, Fang SL, Hinderfeld L, Braverman LE, Vagenatis AG. Effect of starvation, nutrient replacement and hypothyroidism on in vitro hepatic T4 to T3 conversion in the rat. *Metabolism* 1978; 27 : 1680-90.

5. Suda AK, Pitman CS, Shimizu T, Chamber S JB. The production and metabolism of 3,5,3'-Triiodothyronine and 3,3',5' T3 in normal and fasting subjects. *J Clin Endocrinol Metab* 1978; 47 : 1311-8.
6. Kaplan MM, Utiger RJ. Iodothyronine metabolism in rat liver homogenates. *J Clinical Invest* 1978; 61 : 459-71.
7. Saini JS, Naqvi S, Gandhi B, Karnani L. Thyroid hormones in diabetic ketocidosis before and after therapy. *J Assoc Physicians India* 1993; 41 : 415-7.
8. Gilani BB, Margart N, Mac Gillivray, et al. Thyroid hormone abnormalities at diagnosis of insulin dependent diabetes mellitus in children. *J Pediatr* 1984; 105 : 218-22.
9. Postellon CS, Becker DJ, Foley TP. Alteration in triiodothyronine (T3) and reverse triiodothyronine (rT3) concentration in newly diagnosed patients with juvenile diabetes mellitus. *Diabetes* 1978; 27 : 498-501.
10. Saunders J, Hall SEH, Sonksen PM. Thyroid hormones in insulin requiring diabetes before and after treatment. *Diabetologia* 1978; 15 : 29-31.
11. Alexander CJ, Kaptain EM, Lum SMC, Spancer CA, Kumar D, Nicoloff JT. Pattern of recovery of thyroid hormone indices associated with treatment of diabetes mellitus. *J Clin Endocrinol and Metab* 1982; 54 : 362-6.
12. Sheppard MC, Ramsden DS. Thyroid hormones in non-insulin-dependent diabetes before and after dietary treatment. *Clin Endocrinol* 1983; 18 : 593-7.
13. Gavin LA, McMahon TA, Moeller M. Dietary modification of thyroxine deiodination in rat liver is not mediated by hepatic sulfhydryls. *J Clin Invest*. 1980; 65 : 943-6.
14. Kaplan MM. Subcellular alterations cause reduced hepatic thyroxine 5'monodeiodonase activity in fasted rats. *Endocrinol* 1979; 104 : 58-64.
15. Chopra IJ. Alteration in monodeiodination of Iodothyronines in the fasting rat : effects of reduced non-protein sulfhydryl group and hypothyroidism. *Metabolism* 1980; 29 : 161-7.
16. Kabadi VM. Impaired pituitary thyrotroph function in uncontrolled Type II diabetes mellitus : Normalisation on recovery. *J Clin Endocrinol Metab* 1984; 59 : 521-5.
17. Naeije P, Goldstein J, Clumack N, Meinhold H, Wenzel KW, Vauhaelst L. A low T3 syndrome in diabetic ketacidosis. *Clin Endocrinol* 1978; 8 : 467-72.
18. Donders SHJ, Pters GFFM, Haeval JG, Ross HA, Smals AGH, Kloppenbog PWC. Disparity of thyrotropin (TSH) and prolactin responses to TRH in obesity. *J Clin Endocrinol Metabol* 1985; 61 : 56-9.
19. Bhu N, Meena HS, Jailal. Thyroid hormones in non-insulin dependent diabetes mellitus. *J Assoc Physician India* 1988; 36 : 713-4.
20. Lily John, Karunanidhi A, Kanagasabapathy AS. Thyroid function in non-insulin-dependent diabetes mellitus. *J Assoc Physicians India* 1985; 33 : 275-7.