Turkish Journal of Endocrinology and Metabolism, (1999) 4 : 163-168 **ORIGINAL ARTICLE**

The Relationship Between The Glycemic Control and The Hypothalamus-Pituitary-Thyroid Axis in Diabetic Patients

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Diabetes mellitus, similar to other nonthyroidal illnesses, is associated with circadian rhythm abnormalities of serum TSH and thyroid hormones.

In this study, we investigated the effect of good and poor metabolic control on the nocturnal serum TSH peak and the TSH response to TRH stimulation in diabetic patients.32 diabetic patients (type 1, n=9; type 2, n=23; 18 men, 14 women; the mean age: 45.8 (10.5 yrs) with either poor glycemic control (n=22) or good glycemic control (n=10) were enrolled in this study. The nocturnal serum TSH peak (22 ^{30}-02^{00}h) was abolished in the poor glycemic control group, whereas there was a statistically significant peak in the other group (p=0.0001). The morning serum TSH value in the diabetics with the poor glycemic control group did not differ from that in the other group, but the serum TSH and TT4 were significantly higher in the good glycemic control group than the other group and no differences were found in the increase of serum FT4, TT3 and FT3 levels between the two groups after TRH stimulation. The morning serum TT4 and TT3 levels were significantly higher in the good glycemic control group than the other group (p=0.04, p=0.007) whereas the morning serum FT4, FT3 and TSH values did not differ in the two groups. The increase in the serum TSH and TT4 levels after TRH stimulation were significantly higher in the good glycemic control group than the other control group whereas there were no difference in the increase in the serum TT3, FT4 and FT3 levels between the two groups.

In conclusion, metabolic control affects the hypothalamus-pituitary-thyroid axis and the metabolic decompensation in diabetic patients leads to the impairment of TSH secretion,thyroid hormones secretion and their response to TRH.

Key words: TSH, thyroid hormones, glycemic control.

Introduction

Diabetes mellitus has been found to be associated with abnormalities of thyroid function tests; including a decrease in serum total and free T3 concentrations and an increase in serum rT3 levels (1-2). Evaluation of TSH secretion in diabetic patients has provided controversial results. The baseline serum TSH concentration in the morning

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has been reported to be normal or increased (2-4). The serum TSH response to TRH has been found to be either normal or blunted in patients with type I or type II diabetes (2, 4, 5).

The present study was undertaken to evaluate the nocturnal surge of the TSH secretion, the serum TSH and the thyroid hormones' response to TRH in two groups of type I and type II diabetic patients with good and poor glycemic control.

Material and Method

The study group included 32 patients (18 male, 14 female) with either type I (n=9) or type II (n=23) diabetes admitted to the Endocrinology department of Uludağ University. The patients were divided into the good (Group I) and poor (Group II) glycemic control groups. The mean age of the patients with good glycemic control was 44.6±9.6 and the poor glycemic control was 45.9±10.5 years.

No patient had superimposition of an additional illness. All patients were clinically euthyroid. They had no known thyroid disorder, goiter, thyroid-directed autoantibodies, or any drug treatments known to interfere with thyroid function tests. There was no clinical evidence of long term diabetic complications. The diagnosis of diabetes mellitus had been made 1 month to 5 years previously. The patients were either receiving treatment with insulin (12 patients) or oral hypoglycemic drugs (19 patients) or no treatment (1 patient received diet alone).

Blood was drawn in all subjects at 30 minute intervals between 22^{30}-02^{00}h in order to evaluate the TSH secretion, with particular regard to the nocturnal surge of the hormone. In the morning, after baseline TSH, TT4, FT4,TT3 and FT3 determination, the TSH and the thyroid hormones response to i.v. TRH stimulation (200 µg) was assessed by measuring serum TSH and the thyroid hormones 15, 30, 45, 60 and 120 minutes after TRH administration.

Serum TSH was determined by IRMA, serum TT4, FT4, TT3 and FT3 were determined by RIA, fasting glucose, total cholesterol, triglyceride levels by the autoanalyzer Technicon Dax 72, glycosylated hemoglobin (HbA1) concentration by ion-changing colon chromatography.

Normal values of our laboratory are shown in Table 1.

Table 1. Normal values of our laboratory.

TSH	0-6.5 µIU/ml
TT4	4.5-12.5 µg/dl
TT3	95-185 ng/dl
FT4	0.8-2.0 ng/dl
FT3	1.4-4.4 pg/dl
Tcholesterol	143-200 mg/dl
HDL-cholesterol	30-70 mg/dl
Triglyceride	44-148 mg/dl
HbA1	5.5-7.7(%)

Data were expressed as the mean ±SD. Results were analyzed by Variance analysis and "paired" and "paired" Student's t test.

Results

Whereas there was no significant increase in the mean nocturnal levels of serum TSH value in the group with poor glycemic control, there was a significant increase in the group with good glycemic control (p=0.0001).

When the TSH levels of the two groups between 22^{30}-02^{00}h were compared with each other,we demonstrated that the TSH levels in the good glycemic control group were significantly higher tha nin the poor glycemic control group (p=0.0027, p=0.0004, p=0.0001, p=0.0001, p=0.0001 p=0.0001 p=0.0001, p=0.0001).

The mean nocturnal TSH level was significantly higher than the baseline level in the morning in the good glycemic group (p=0.0001) (Table 2).

Table 2. The comparison of the night and morning baseline TSH levels between the groups with good (Group I) and poor (Group II) glycemic control.

TSH (µIU/ml)	Group I n=10	Group II n=22	p
Night	2.88±0.32	1.32±0.75	0.006
Morning	0.72±0.46	0.98±0.52	0.17
p	0.0001	0.5	

here was no significantbetween the mean nocturnal TSH level and the morning baseline TSH levels in the poor glycemic control group (p=0.5) (Table 2).

While there was no significant difference between the morning baseline TSH levels of the good and poor glycemic control groups,the TSH response to TRH in the 15., 30., 45. and 120. minute was significantly higher in the good glycemic control group than in the poor glycemic control group (p=0.0221, p=0.0114, p=0.0427, p=0.039).

The serum baseline morning TT4 and TT3 levels were higher in the group with good glycemic control than in the poor glycemic control group (p=0.04, p=0.007) (Table 3).

Table 3. The comparison of the morning baseline levels TT4, TT3,FT4 and FT3 between the group with good (Group I) and poor (Group II) glycemic control.

TSH (µIU/ml)	Group I n=10	Group II n=22	p
TT4 (µg/dl)	9.3±1.41	6.81±1.97	0.007
TT3 (ng/dl)	16.6±25.1	98.6±20.52	0.04
FT4 (ng/dl)	1.12±0.24	0.99±0.2	0.12
FT3 (pg/dl)	2.48±1.13	2.03±0.62	0.28

When the response of the TT4, TT3, FT4 and FT3 to TRH in the 120 th. minute in the groups with good and poor glycemic control were compared with each other, the TT4 level in the group with good glycemic control was higher than the poor glycemic control group (p=0.04) (Table 4).

The TT4, TT3 and FT3 responses to TRH in the 120 th. minute were significantly higher than their baseline morning levels in the group with poor glycemic control (p=0.03, p=0.0001, p=0.0001) (Table 5).

Table 4. The comparison of the serum TT4, TT3, FT4 and FT3 response to TRH between two groups with good (Group I) and poor(Group II) glycemic control.

120th min.	Group I	Group II	p
TT4	8.61±1.36	7.36±1.6	0.04
TT3	125.8±27.68	135.54±19.9	0.26
FT4	1.17±0.29	1.05±0.2	0.18
FT3	2.64±0.96	2.87±0.84	0.49

Discussion

In various studies the abnormalities of TSH and thyroid hormone secretion have been shown in patients with diabetes mellitus, similar to other nonthyroidal illnesses (2, 4-9). These changes were in relation with the alteration of all levels of the thyroid-pituitary-hypothalamic axis (6, 10-22). In these studies it has been observed that the levels of serum TT4 and TT3 may be low or normal, levels of rT3 may be high or normal, the nocturnal peak of TSH secretion is blunted or abolished, the serum baseline TSH secretion in the morning may be normal, low or high and the serum TSH response to TRH may be normal or blunted in patients with diabetes mellitus (23-36).

In our study, when patients were evaluated in two groups according to the glycemic control criteria without taking their diabetes type into consideration; poor and good glycemic control group, it is demonstrated that the nocturnal peak of the TSH levels between the ours 22^{30} p.m. and 02^{00} a.m. was blunted and that the TSH levels between the same hours did not differ from each other in the poor glycemic control group whereas the normal

Tablo 5. The comparison of the serum baseline levels of TT4, TT3, FT4 and FT3 and their response to TRH between the groups with good (Group I) and poor (Group II) glycemic control.

	GROUP I			GROUP II		
	Basal	120^{th} min	p	Basal	120^{th} min	p
TT4 (µg/dl)	9.3 ± 1.41	8.61 ± 1.36	0.06	6.81 ± 1.97	7.36 ± 1.6	0.03
TT3 (ng/dl)	11.6 ± 25.1	125.8 ± 27.68	0.07	98.6 ± 20.52	135.54 ± 19.9	0.0001
FT4 (ng/dl)	1.12 ± 0.24	1.17 ± 0.29	0.64	0.99 ± 0.2	1.05 ± 0.2	0.08
FT3 (pg/dl)	2.482 ± 1.13	2.64 ± 0.96	0.76	2.03 ± 0.62	2.87 ± 0.84	0.0001

physiological peak was seen in the good glycemic control group. When the serum TSH levels between these hours of the poor glycemic group were compared with the levels of the good glycemic control group, there was no difference between them. The poor metabolic control in diabetic patients leads to an impairment of TSH secretion. Schmitz et al. observed an acute depression of serum TSH levels at night in type I diabetic patients and attributed it to ketoacidosis in view of the correlation of changes in TSH levels with the increase in blood 3-hydroxybutyrate levels (24). Bartalena et al. demonstrated that not only type I, but also type II diabetes were associated with the lack of a nocturnal TSH peak when diabetes was poorly controlled (2). Our results are in agreement with these reports.

In our study the serum baseline TSH levels in the morning did not differ in the two groups. When the serum baseline TSH levels in the morning are compared with the nocturnal serum TSH levels in both groups, the levels in the morning in the good glycemic control group are significantly higher than the levels in the poor glycemic control group. This result leads us to the conclusion that the abolishment of the nocturnal TSH peak in the poor glycemic control group reflects the baseline TSH levels in the morning. Bartalena et al. have shown that the mean serum TSH values at night did not differ from the morning value in diabetics before correction of hyperglycemia and posttreatment serum TSH levels, both at night and in the morning, did not differ from the respective values in normal controls (2). Naeije et al. observed that the baseline serum TSH levels were low in diabetic patients with poor glycemic control; Baldet et al. and Mac Farlane et al. found it normal and Alexander et al high (20, 23, 25, 26).

In our study the baseline serum TT4 levels were normal in the good glycemic control group, whereas they were found low in the poor glycemic control group. It would appear that the alterations in the circadian rhythm of TSH and the abolishment of the nocturnal TSH peak are associated with the result where TT4 to is low. Chopra et al. suggested that the low TT4 in nonthyroidal illness is a result of decreased binding of thyroid hormones and that the serum free T4 was normal or high with low TT4 because the dialyzable fraction of T4 was generally high. (37) Other studies of poorly controlled diabetics have found serum T4 levels to be low or normal (18, 20, 27) but they suggested that these differences probably reflect the varying severity of metabolic derangement in the groups of patients studied (18, 27).

The baseline serum TT3 levels were lower in the poor glycemic control group than in the good glycemic control group. These changes are largely due to reduced conversion of T4 toT3 consequent on impaired activity of 5'-deiodinase (37). Bagchi et al. suggested that in addition to central changes, diabetes may be associated with a primary impairment of hormone secretion from the thyroid which would normalize upon control of hyperglycemia (33) and that this was related to impaired hydrolysis of thyroglobulin which occurred even when adequate (exogenous) TSH was administered (13). Pittman et al. observed that in the diabetic subjects there was a significant correlation between reduced T3 production and impairment of glucose uptake and utilization (5).

The TSH response to TRH administration is blunted in the poor glycemic control group. This result is in agreement with previous reports from other groups (2, 6, 7, 23). Mac Farlane et al. thought that despite subnormal circulating T3 concentrations baseline and TRH stimulated TSH secretion was unaffected because of normal circulating T4 concentrations (23). Their conclusion lends support to the hypothesis of Larsen in which a significant proportion of the intracellular T3 available for nuclear receptor binding was derived from deiodination of T4 within the pituitary (23).

In our study the TT4 and TT3 increase after i.v. TRH administration was significantly higher in the poor glycemic control group than the good glycemic control group.In the study of Mac Farlane et al. the T3 increment after TRH test was normal throughout, indicating no change in relative TSH immunological and biological activity (23). They suggested that in association with the poor TSH response to TRH, the T3 increment was reduced

due to the severity of the diabetic state. Azukizawa et al. reported that increments of serum TSH greater than 5 µU/ml were followed by increments in both circulating T3 and T4 and that there were no significant increments in plasma thyroid hormone concentration following the nocturnal TSH surge (38).

In conclusion, metabolic control is associated with the hypothalamus-pituitary-thyroid axis and the metabolic decompensation in diabetic patients leads to the impairment of TSH secretion, thyroid hormones secretion and their response to TRH.

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