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EUTHYROID SICK SYNDROME IN TYPE I DIABETES MELLITUS IN CHILDREN AND ADOLESCENTS*

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We studied concentrations of thyroid hormones (T_3, T_4, FT_4, rT_3, TBG and TSH) in 62 type I diabetic children and adolescents. The patients were classified into group A (n = 27, good control, HbA_{1c}<10 %), group B (n = 19, poor control, HbA_{1c}>10 %) and group C (n = 16, diabetic ketoacidosis, pH <7.1 and HCO_3 <15 mmol/L. All patients were treated with two daily injections of purified monocomponent insulins. Thirty healthy subjects of the same age served as control group. Patients in group B and C had significantly lower T_3 and higher rT_3 levels ($p < 0.001$) compared to the matched controls (1.5 vs 2.2; 0.9 vs 2.2; 0.58 vs 0.3 and 0.6 vs 0.3 nmol/L). Serum TBG levels were significantly lower ($p < 0.01$) in the group A (19.5 $\pm$ 4.3 mg/L), group B (20.3 $\pm$ 3.3) and group C (18.0 $\pm$ 3.4) compared with control group (24.2 $\pm$ 3.1). There was significantly negative correlation between T_3 and HbA_{1c} in group B ($r = 0.546$; $p < 0.02$). The results of this study confirm that euthyroid sick syndrome does exist in type I diabetic children and adolescents with poor metabolic control and ketoacidosis. The inverse relationship between T_3 and HbA_{1c} percentage (low T_3 and high HbA_{1c}) points to the poor diabetic control.

INTRODUCTION

The biochemical changes in circulating thyroid hormones, described as euthyroid sick syndrome /5/ have been observed in uncontrolled type I diabetic children and adolescents /2,3,4/.

It is well recognised that deficiency of insulin, disordered glucose metabolism and ketoacidosis are accompanied by

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alternation in the peripheral metabolism of thyroid hormones /1,3,7/. Pittman et al /9/ have suggested that T_3 production from peripheral T_4 monodeiodination is impaired in uncontrolled diabetic patients.

In the present study we investigated circulating thyroid hormone concentrations, thyrotropin (TSH) and thyroxine binding globulin (TBG) in various stages type I diabetes in children and adolescents.

PATIENTS AND METHODS

Sixty-two type I diabetic children and adolescents were studied. The patients were classified into three groups according to the results of diabetic control. The diabetic patients were treated by two daily injections of purified monocomponent insulins (Actrapid MC and Monotard MC, Novo Industri, Copenhagen).

Group A comprised 27 patients (14 females and 13 males; 12 prepubertals and 15 pubertals) aged 4.5 to 16 years (mean 11.5 years), body weight from 15 to 49 kg (mean weight 28.3 $\pm$ 6.2), body height from 108 to 158 cm (mean height 130.2 $\pm$ 12.0). The glycosylated haemoglobin (HbA_{1c}) amounted from 5.5 to 10 % (mean 8.3 %).

Group B comprised 19 patients (9 females and 10 males; 7 prepubertals and 12 pubertals) aged 7 to 16 years (mean 12.7 years), body weight from 20 to 50 kg (mean weight 30.2 $\pm$ 6.8 kg), body height from 122 to 155 cm (mean height 133.1 $\pm$ 11.5 cm). The HbA_{1c} amounted from 11.1 to 19.3 % (mean 14.7 %).

Group C consisted of 16 diabetic ketoacidosis patients (10 females and 6 males; 6 prepubertals and 10 pubertals) aged 5.5 to 16 years (mean 12.6 years), body weight from 16 to 45 kg (mean weight 26.2 $\pm$ 4.4 kg), body height from 115 to 152 cm (mean height 131.2 $\pm$ 10.2 cm). The arterial pH values amounted from 6.9 to 7.3 (mean 7.1) and serum bicarbonate levels from 2.2 to 16 mmol/L (mean 9.8 mmol/L). The control group consisted of 30 normal children and adolescents (16 females and 15 males; 13 prepubertals and 17 pubertals) aged between 6 to 14 years (mean 10.1 years), body weight from 14 to 55 kg (mean 33.3 $\pm$ 15.0 kg), body height from 105 to 165 cm (mean 135.0 $\pm$ 15.0 cm).

All the subjects examined were clinically euthyroid. After an overnight fast, cannulation of an antecubital vein blood was taken for hormone estimations. The thyroid hormones were measured by specific radioimmunoassay. Total serum triiodothyronine (T_3) and thyroxine (T_4) levels were measured with reagents provided by the Institute for Nuclear Sciences "Boris Kidrič" in Vinča. Serum free thyroxine (FT_4) was determined by RIA-cot (Mallinckrodt Diagnostica,

Dietzenbach) and reverse T_3 (rT_3) was detected by Reverse T_3 kit (Biodata, Roma). The RIA-h-TBG set and RIA-h-TSH set (INEP, Zemun) were used for detecting the TBG and the TSH. HbA_{1c} values were determined with chromatography on a BIO-RAD column. Total biocarbonate and pH were measured by standard Technicon Autoanalyser methods.

The statistical analysis was performed by student's t-test. Correlation coefficients were calculated by regression analysis. All data were represented as the mean $\pm$ 1 SD.

RESULTS

The serum levels of thyroid hormones, TSH and TBG in the diabetic patients and normal controls are summarized in Table I. Patients in groups B (poor control) and C (diabetic ketoacidosis) had significantly lower T_3 and higher rT_3 levels ($p < 0.001$) compared to the matched control subjects. Serum TBG levels were significantly lower ($p < 0.01$) in the group A, B and C in comparison with those found in the control group. Patients in group C had significantly lower T_4 levels ($p < 0.001$) than normal subjects. A negative correlation was found between T_3 and HbA_{1c} in group B (poor control) with significance ($r = -0.546$; $p < 0.02$) (Fig. 1).

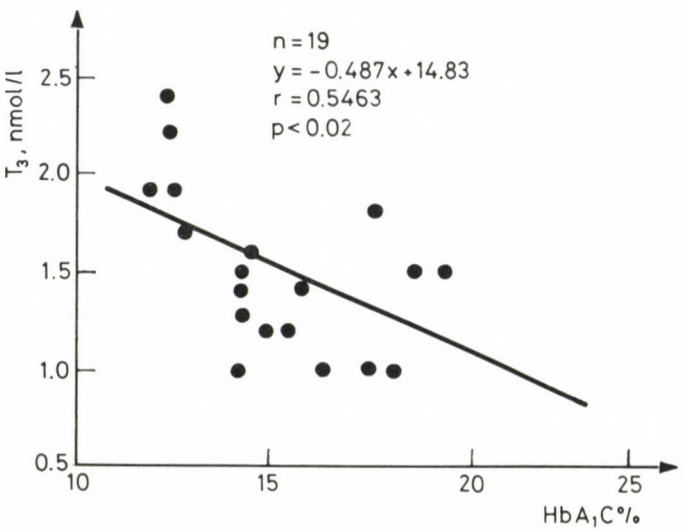

Fig. 1. Correlation between serum T_3 levels and the percentage of HbA_{1c} in diabetic patients with poor control

TABLE I

Serum hormone levels in euthyroid sick syndrome in type I diabetes mellitus in children and adolescents[1]

	T_3 (nmol/L)	T_4 (nmol/L)	FT_4 (nmol/L)	rT_3 (nmol/L)	TSH (nmol/L)	TBG (nmol/L)
Healthy subjects (n = 30)	2.2 (± 0.5)	108.0 (±29.0)	20.1 (± 4.9)	0.3 (± 0.1)	2.4 (± 1.5)	24.2 (± 3.1)
Group A: good control (n = 27)	2.0 (± 0.5	103.0 (±23.8)	22.4 (± 4.4)	0.3 (± 0.2)	2.0 (± 1.3)	19.5 (± 4.3)[x]
Group B: poor control (n = 19)	1.5 (± 0.4)[*]	108.0 (±24.4)	20.4 (± 4.0)	0.58 (± 0.2)[*]	2.3 (± 2.8)	20.3 (± 3.3)[x]
Group C: ketoacidosis (n = 16)	0.9 (± 0.3)[*]	81.9 (±24.2)[*]	18.6 (± 8.8)	0.6 (± 0.1)[*]	2.6 (± 1.8)	18.0 (± 3.8)[x]

[1] Results are expressed as mean ± SD

[x] $p < 0.01$

[*] $p < 0.001$: compared to healthy subjects

DISCUSSION

The values for T_3 and rT_3 found in diabetic patients with poor control and diabetic ketoacidosis are similar to those obtained in other studies in adults and juvenile type I diabetes /4,6,7,8,10,11/, and provide further evidence for an impairment in 5 monodeiodinase activity which controls the peripheral conversion of T_4 into T_3 and catabolism of rT_3 /12/. The inverse relationship between T_3 and HbA_{1c} (low T_3 and high HbA_{1c} values) shows that changes in thyroid hormone peripheral metabolism are related to the degree of impaired glucose utilization. These results are consistent with those of Dorchy et al /4/ and Salardi et al /11/ who found a significant negative correlation between T_3 and HbA_{1c} in the poorly controlled juvenile type I diabetic patients.

We found no difference between the serum T_4 and FT_4 levels in patients with good and poor control in comparison to the control group. Other studies of poorly and good controlled diabetics have shown serum T_4 concentrations to be low /10/ or not different from the control group /4/. However, our results for FT_4 are consistent with those of Radetti et al /10/ and Dorchy et al /4/ who found no difference between diabetic patients and controls.

The significant decrease of T_3 and T_4 serum concentrations as well as the significance increase of serum rT_3 levels in our patients with diabetic ketoacidosis are similar to those obtained in other studies /8,11/. These findings suggested that diabetic children and adolescents with ketoacidosis present an euthyroid sick syndrome. Therefore, we support the assumption of Castels /3/ that ketoacidosis has an inhibitory effect on peripheral conversion of T_4 to T_3, being thus responsible for disturbances in thyroid hormone blood level in these states.

Despite significant decrease of serum T_3 levels, basal TSH concentrations in our patients were normal. This suggests that circulating T_4 by its free fraction may have an important impact on the regulation of TSH secretion /6/, to which our FT_4 findings are confirmatory.

In conclusion, this study has shown that children and adolescents with poorly controlled diabetes and ketoacidosis exert an euthyroid sick syndrome. Thus, the thyroid hormones may be an important indicator of metabolic status in the diabetic children and adolescents.

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