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Rom J Diabetes Nutr Metab Dis. **22**(4):411-418
doi: 10.1515/rjdnmd-2015-0048

ANTITHYROID THERAPY IMPROVES GLYCEMIC CONTROL IN HYPERTHYROID TYPE 1 DIABETES MELLITUS PATIENTS

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received: October 15, 2015 *accepted*: November 27, 2015
available online: December 15, 2015

Abstract

Background and aims. *Thyroid disorders are more frequently met in patients with diabetes mellitus than in general population. Thyroid hormones increase glycemia by several mechanisms, but the effect of antithyroid treatment on glucose control in type 1 diabetes mellitus (T1DM) cases is not well studied. The aim of our work was to analyze the evolution of glycemic control of T1DM patients submitted to specific therapy when hyperthyroidism was diagnosed.* **Material and method.** *The study group comprised by 37 patients, 35 women (94.6%) and 2 men (5.4%), known as having T1DM and diagnosed with hyperthyroidism during a 10-years interval. They were treated with antithyroid medication and reassessed after 6 months regarding thyroid function and glycemic control.* **Results.** *In the whole group, there was a significant decrease in mean HbA_{1c} level (with 0.41%) and a significant increase in the percentage of patients being in the glycemic target (from 10.8% to 35.1%). The better glycemic control was obtained with a lower mean insulin dose. Patients who became euthyroid had a better evolution regarding glucose control in comparison to those who remained hyperthyroid. Changes in other cardiovascular risk factors were noted: systolic blood pressure decreased; diastolic blood pressure, HDL cholesterol, LDL cholesterol, non-HDL cholesterol, triglycerides and body weight increased. TSH and HbA_{1c} values were inversely correlated.* **Conclusions.** *The therapeutic control of excessive thyroid function significantly contributes to the improvement of glycemic control in patients with T1DM and induces changes in the cardiovascular risk factors profile.*

key words: *type 1 diabetes mellitus, hyperthyroidism, glycemic control.*

Background and Aims

Thyroid dysfunction and diabetes mellitus (DM) are two conditions encountered frequently in clinical practice. They may co-exist and many authors found a higher prevalence of thyroid disorders in patients with DM, both type 1 (T1DM) and type 2, as compared to the general population. The prevalence of thyroid dysfunction in adult population from normal iodine intake regions was found to vary between 6.6 and 8.8% in different studies [1-3]. This is higher (between 10.8 and 13.4%, according to the source) in adult patients with DM [4,5]. Women with T1DM have the highest prevalence

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(31.4%), and men with type 2 DM the lowest (6.9%) [4].

The occurrence of hyperthyroidism in patients with DM was found to be higher than in general population: Perros et al [4] reported a 1% incidence of hyperthyroidism in cases with DM while in the Whickham survey, the incidence of hyperthyroidism was estimated at 0.3% in the general adult population [1]. Graves' disease and toxic nodular goiter are the most frequent causes of hyperthyroidism [6].

Thyroid hormones in excess promote hyperglycemia by several mechanisms [6-9]: increased glucose absorption in the bowel, impaired insulin secretion, accelerated insulin degradation, elevation of glucagon levels, increased hepatic glucose production, insulin resistance and, possibly, hypercathecol-aminemia. In other words, in hyperthyroidism there is a high glucose output from the liver and a diminished action of insulin. In untreated Graves' disease, increased proinsulin levels in response to meals and a reduced ratio between C-peptide and proinsulin were observed, suggesting a defect in proinsulin processing [10,11].

Undiagnosed thyroid dysfunction may affect metabolic control in patients with DM and even favor the occurrence of ketoacidosis [12,13]. In some conditions, this association may raise the already increased risk for cardiovascular diseases of these patients [14].

The purpose of this paper was to analyze the evolution of glycemic control, as well as of other clinic and biologic parameters, in patients with T1DM and hyperthyroidism subjected to antithyroid therapy.

Material and method

Patients

This is a retrospective study that included 37 patients, 35 women (94.6%) and 2 men (5.4%), aged 18 to 58 years, all previously diagnosed with T1DM, who were treated in the Department of Endocrinology of the County Emergency Hospital Timisoara between March 2003 and March 2013 for overt hyperthyroidism. The diagnosis was based on hormonal measurements (TSH, FT_4 ± FT_3). The study protocol and procedures were approved by the local Ethics Committee. All the subjects were treated for hyperthyroidism with methimazole and were reassessed after six months, by repeating the hormonal and biochemical tests performed at baseline. We mention that insulin therapy was administered according to the rules of medical practice: all patients received basal-bolus regimen, had frequent blood glucose measurements, and insulin dosage was adjusted according to blood glucose values.

Clinic and laboratory measurements

The following data were retrieved from the medical records of the patients: age, DM duration, height, weight and blood pressure. Body mass index (BMI) was calculated. The following biologic parameters were measured in fasting condition (at least 8 hours after the last meal): TSH, FT_3, FT_4, HbA_{1c}, lipids (total cholesterol, LDL cholesterol – LDLc, HDL cholesterol – HDLc, triglycerides – TG) and glycemia. TSH, FT_3 and FT_4 were assessed using ECLIA (electro-chemiluminescence method) having the following reference range: 0.27 – 4.20 µUI/mL for TSH, 3.9 – 6.7 pmol/L for FT_3 and 12.0 – 22.0 pmol/L for FT_4. A patient was considered to present overt hyperthyroidism if TSH was suppressed and FT_4 and/or FT_3 increased. In all patients thyroid ultrasonography was performed and in 28 patients (75.7%) TSH-receptor antibodies were determined in order to confirm the diagnosis of Graves' disease.

Statistical analysis

Data were analyzed using SPSS version 17 (SPSS, Chicago, IL) and are presented as means ± standard deviations for continuous, normally distributed variables, medians and interquartile ranges for continuous not-normally distributed values and percentages for categorical parameters. In order to assess the significances of the differences, paired t-test was used for two means of paired series. Continuous variables distributions were tested for normality using D'Agostino-Pearson omnibus test and for homoscedasticity with Levene's test. The interrelation between continuous variables was assessed using correlation and regression analysis; its strength was evaluated using Pearson's correlation coefficient and of which statistical significance was calculated with t-value rank distribution test. The significance of differences between proportions was assessed using Fisher's exact test. A p value <0.05 was considered statistical significant.

Results

The baseline characteristics of these patients are presented in Table 1.

Table 1. Baseline characteristics of patients with T1DM and hyperthyroidism.

Parameter	Result
Number of patients	37
Age (years) [a]	36 [18]
DM duration (years) [a]	8 [6]
BMI (kg/m^2) [b]	22.4 ± 3.8
Medication used during the study [c]	
-methimazol	37 [100]
-insulin	37 [100]
-betablockers	37 [100]
-ACE inhibitors	7 [18.9]
-statins	6 [16.2]
-anxiolytics	23 [62.2]

Legend: ACE=angiotensin converting enzyme; [a]=variables are not-Gaussian distributed and are presented as median and [interquartile range]; [b]=variables are normally distributed and are presented as mean ± standard deviation; [c]=data are presented as number [percent].

After six months of therapy, thyroid function became normal in 25 patients (67.6%). For the entire study group, we observed a significant decrease in HbA_{1c} level (0.41 ± 0.34%; p <0.001) and systolic blood pressure (5.4 ± 7.0 mmHg; p <0.001). Increases were recorded for TG (12.9 ± 14.4 mg/dL; p<0.001), HDLc (2.0 ± 2.4mg/dL; p<0.001), LDLc (5.9 ± 4.9 mg/dL; p<0.001), non-HDLc (8.5 ± 6.2 mg/dL; p <0.001), body weight (2.6 ± 2.2 kg; p = 0.004) and diastolic blood pressure (2.2 ± 3.9 mmHg; p=0.002). Mean blood pressure showed no significant changes (from 98.3± 11.8 to 98.7 ± 12.3mmHg; p = 0.57). The results are shown in Table 2.

Table 2. Clinic and biologic characteristics of the study group before and after antithyroid therapy.

Parameter	Before treatment	After treatment	P
TSH (µUI/mL)	0.011 ± 0.013	1.946 ± 1.503	<0.001*
FT_3 (pmol/L)	15.6 ± 19.7	5.2 ± 1.9	0.0025*
FT_4 (pmol/L)	36.0 ± 10.3	17.8 ± 4.2	<0.001*
HbA_{1c} (%)	7.93 ± 0.69	7.52 ± 0.76	<0.001*
Daily insulin dose (UI/kg)	0.83 ± 0.38	0.68 ± 0.31	<0.001*
LDLc (mg/dL)	94.9 ± 10.6	100.8 ± 12.4	<0.001*
HDLc (mg/dL)	42.5 ± 4.7	44.5 ± 4.7	<0.001*
non-HDLc (mg/dL)	124.9 ± 12.7	133.5 ± 15.6	<0.001*
TG (mg/dL)	150.3 ± 25.9	163.2 ± 29.0	<0.001*
Body weight (kg)	56.2 ± 6.3	58.8 ± 8.2	0.004*
SBP (mmHg)	124.2 ± 12.2	118.8 ± 14.1	<0.001*
DBP (mmHg)	56.9 ± 8.5	59.1 ± 8.4	0.002*
MBP (mmHg)	98.3 ± 11.8	98.7 ± 12.3	0.57

Legend: *=differences are significant; SBP=systolic blood pressure; DBP=diastolic blood pressure; MBP=mean blood pressure.
p-value was assessed using paired t-test. Variables were tested for normality using D'Agostino-Pearson test and for homoscedasticity using Levene's test

After antithyroid treatment, the proportion of patients reaching good glycemic control

(HbA_{1c}<7%) increased significantly, from 10.8% to 35.1% (p=0.025).

The improvement in glucose control was obtained in the conditions of the reduction of the mean daily dose of insulin from 0.83 IU/kg body weight to 0.68 IU/kg body weight.

The analysis on subgroups (patients who became euthyroid after therapy versus patients who remained hyperthyroid) showed a better evolution of glucose control in the first subgroup: HbA_{1c} presented a more important reduction (0.54 ± 0.29% vs. 0.13 ± 0.28%; p <0.001), and the percentage of patients that reached the target for glycemic control was higher (44% v. 16.7%, p = 0.149). After 6 months of treatment, when compared to hyperthyroid patients, the euthyroid group was associated with a lower HbA1c (7.22% vs. 8.15%, p <0.001) and daily insulin dose (0.61 UI/kg vs. 0.82 UI/kg, p <0.001), higher triglycerides (172.56 mg/dL vs. 128.47 mg/dL, p=0.001) and body weight (60.3 kg vs. 55.7 kg, p<0.001). The differences in the other studied parameters had no statistical significance (Table 3).

Table 3. Studied parameters after 6 months of treatment. Comparison between the groups of patients which reached euthyroid status vs. patients still with hyperthyroidism.

Parameter	Euthyroid patients (n=25)	Hyperthyroid patients (n=12)	P
TSH (µUI/mL)	2.71 ± 1.21	0.35 ± 0.27	<0.001*
FT_3 (pmol/L)	4.54 ± 0.89	6.45 ± 2.91	0.046 *
FT_4 (pmol/L)	16.8 ± 3.66	20.0 ± 4.47	0.027 *
HbA_{1c} (%)	7.22 ± 0.49	8.15 ± 0.85	<0.001 *
Daily insulin dose (UI/kg)	0.61 ± 0.28	0.82 ± 0.36	<0.001 *
LDLc (mg/dL)	101.36 ± 10.97	99.75 ± 15.45	0.717
HDLc (mg/dL)	45.36 ± 4.65	42.58 ± 4.50	0.096
non-HDLc (mg/dL)	135.87 ± 14.28	128.47 ± 17.76	0.223
TG (mg/dL)	172.56 ± 28.19	143.58 ± 20.17	0.001 *
Body weight (kg)	60.3 ± 9.4	55.7 ± 5.7	<0.001 *
SBP (mmHg)	118.24 ± 13.08	120.0 ± 16.52	0.750
DBP (mmHg)	57.76 ± 7.11	61.83 ± 10.50	0.173
MBP (mmHg)	97.17 ± 10.80	101.83 ± 15.04	0.350
Legend: *=differences are significant			

We observed a moderate, negative, statistically significant correlation between TSH and HbA_{1c} levels after treatment, for the whole group (r = –0.60 [95% CI –0.77 to –0.35], p <0.001) (Figure 1).

Furthermore, the increases in TSH value, obtained after treatment, reverse correlated significantly with the differences in HbA1c (ΔHbA1c = HbA1c after treatment – HbA1c prior treatment), meaning that a more important increase in TSH values leads to a more significant improvement in glycemic control (r= -0.37 [95% CI -0.62 to -0.05], p=0.023) (Figure 2).

Discussions

A lot of clinical trials performed in patients with type 1 [15,16] and type 2 DM [17,18] have clearly proven that a better glycemic control has beneficial effects on long term prognosis, by reducing the incidence and progression of chronic complications, mainly microvascular and neuropathic. HbA_{1c} is the primary target for evaluating glycemic control. Goals should be individualized based on patient's age, DM duration, life expectancy, presence of comorbid conditions and complications of DM, compliance and risks related to hypoglycemia. For the majority of patients, the target value for HbA_{1c} is less than 7% or 53mmol/mol [19,20].

There are many factors that influence the quality of glucose control. Some of them depend on the patient (education, self blood glucose monitoring, compliance to therapy, motivation,

resources), some on the medical system (ability of the physician to prescribe an adequate insulin regimen and to transmit to the patient the medical information required, availability of modern and efficient methods of insulin therapy) and, finally, others to DM itself or to associated diseases. Hyperthyroidism is such a condition. Its presence usually increases glycemic values. The mechanisms are multiple and some become obvious only in patients with DM [21]. In clinical practice it represents a condition that may explain why insulin requirement increases and glycemic control worsens in a patient with DM, or may even precipitate the occurrence of diabetic ketoacidosis [12,13].

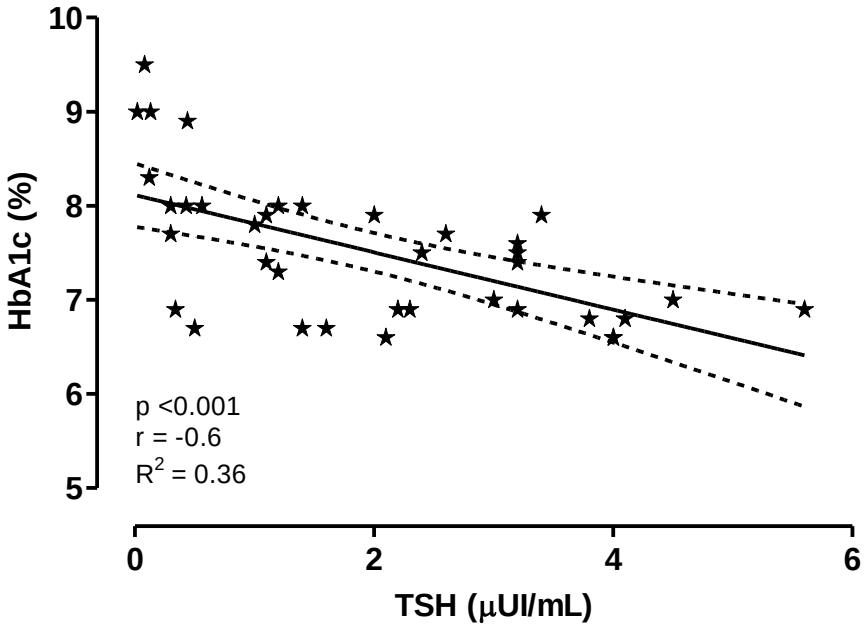

Figure 1. *The relationship between TSH and HbA_{1c} after six months of treatment.*

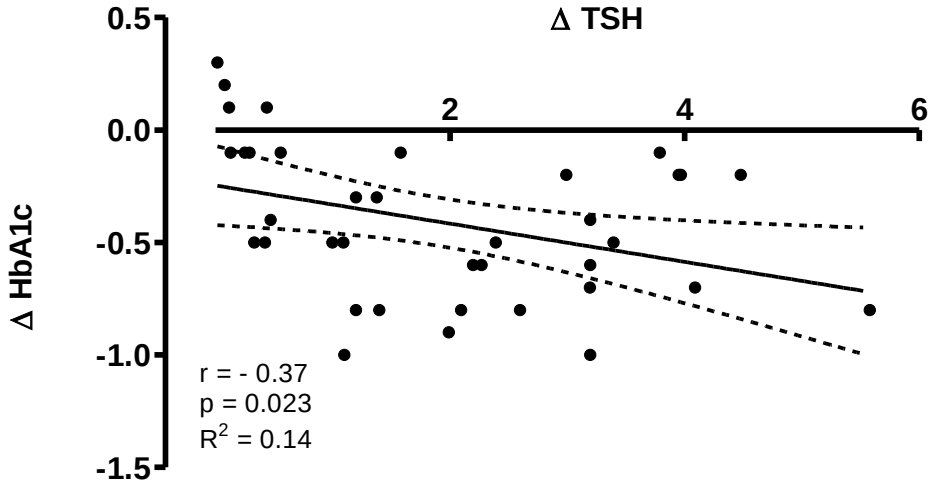

Figure 2. *The association between the increases in TSH and decreases in HbA1c, after 6 months of treatment.*

According to our knowledge, there are few data in the literature that analyze the evolution of the patients with DM in case of coexistence of hyperthyroidism [22], none of them for the

Romanian population that is living in a region with adequate iodine intake, as indicated by previous studies, and has an increasing incidence of hyperthyroidism in the last years [23,24].

In our study, HbA_{1c} decreased after 6 months of antithyroid therapy, mainly in patients who became euthyroid. There are several explanations for the good evolution of glycemic control. The first one is the therapeutic control of thyroid function that acts by multiple mechanisms, discussed previously. Second, patients with hyperthyroidism have an increased appetite and, in the case of coexistence of DM, this contributes to the glycemic disequilibrium. By compensating the thyroid function, the appetite decreases, fact that presumably contributes to a better glycemic control. However, there are no data regarding the evolution of the caloric intake of our patients during the study. Finally, the compliance to therapy is highly variable. One can assume that patients who became euthyroid under specific treatment might have been more compliant to antithyroid therapy (and insulin regimen, as well) and that could have led to a better glycemic control. All the 37 patients analyzed in this paper had been diagnosed with T1DM before hyperthyroidism and were on a stable therapeutic regimen. Their adherence to the medical recommendations was probably the same before and during the follow-up period. That's why we consider that changes in glycemic control were due mainly to antithyroid therapy.

Our results indicate that correction of hyperthyroidism induced an improvement of glycemic control, in the condition of a reduction in insulin dose, underlined by a significant decrease of HbA_{1c} (with 0.41%) and an increase in the number of patients that reached the main glycemic target (from 10.8% to 35.1%). This value may seem not clinically relevant, but it is well known that in T1DM patients improvement of HbA_{1c} has benefits on long term [15] and that it is preferable to obtain a good glycemic control early in the course of the disease, because this influences the occurrence of complications, as well [16]. The reduction of HbA_{1c} was more important in the subgroup of patients who became euthyroid after 6 months of therapy. Furthermore, the percentage of patients that reached the target for HbA_{1c} was higher in this group (the differences did not reach the threshold for significance for this parameter due to the relative small number of subjects included in the study).

The negative, statistically significant correlation found between TSH and HbA_{1c} after hyperthyroidism treatment, confirms the influence of this therapy on the quality of the glycemic control.

After correction of hyperthyroidism, significant changes in some cardiovascular risk factors were noted, leading to changes in the risk profile of the patients: LDLc, non-HDLc, TG, diastolic blood pressure and body weight increased, worsening the cardiovascular prognosis; HDLc augmented and systolic blood pressure decreased, with favorable consequences on cardiovascular profile; mean blood pressure remained, practically, unchanged. Since the therapy with statins and antihypertensive agents has not been modified during the follow-up, the changes of the aforementioned parameters could be explained only by the influence of the thyroid hormones and glycemic control. The increase of the cholesterol fractions (HDLc, non-HDLc and LDLc) was induced mainly by the correction of hyperthyroidism, being known that the thyroid hormones are involved in the metabolism of cholesterol by several mechanisms [25]: they increase the expression of both 3-hydroxy-3-methyl-glutaryl-CoA reductase and LDL receptors. The TG values are influenced by both

glycemic control and thyroid function (thyroid hormones activate the enzyme lipoprotein lipase, responsible for the catabolism of TG-rich lipoproteins). In general, they decrease in parallel with the reduction of HbA_{1c} in patients with DM and increase when hyperthyroidism is compensated under specific therapy. In our patients, the increase in TG could be explained by the more pronounced influence of the improvement of thyroid function than of the glycemic control. The evolution of the overall global risk for cardiovascular diseases is difficult to be evaluated in these circumstances. Even if cardiovascular risk would have increased after antithyroid therapy, the treatment of hyperthyroidism is worth even judged by this perspective: it is known that uncontrolled thyroid function means a higher risk of cardiovascular morbidity and mortality, mainly due to arrhythmias [26,27].

Our work has some strengths: it is the first paper that analyses the evolution of the glycemic control under antithyroid therapy in Romanian patients with T1DM and hyperthyroidism; all the patients were treated for DM in a Diabetes Center by highly qualified medical staff; the patients were on a stable therapeutic regimen for DM, so that this did not exert an important influence on the glycemic control once antithyroid therapy was started. There are some limitations, as well: this was a retrospective study; the patients were not followed-up in accordance to a standardized protocol; there is no accurate information regarding the caloric intake and the compliance to antidiabetic and antithyroid therapy; the majority of the patients were women, due to the fact that Graves' disease is much more prevalent in women than in men. The question that remains unanswered after this analysis is related to the possible influence of the diet, in addition to antithyroid treatment, on the improvement of glycemic control.

Conclusions

To conclude, our study confirms that the therapeutic control of increased thyroid function contributes significantly to the improvement of glycemic control and changes the profile of cardiovascular risk factors of the patients. Due to the fact that thyroid dysfunction is quite frequently encountered in T1DM patients and that the correction of hyperthyroidism represents a method for improving glycemic control (in addition to the other known benefits), screening tests for thyroid function should be periodically performed in every patient with T1DM.

Conflict of interests. The authors declare no conflict of interest regarding this work.

REFERENCES

1. **Tunbridge WM, Evered DC, Hall R et al.** The spectrum of thyroid disease in a community: the Whickham survey. *Clin Endocrinol* 7: 481-493, 1977

2. **Canaris GJ, Manowitz NR, Mayor G, Ridgway EC.** The Colorado thyroid disease prevalence study. *Arch Intern Med* 160: 526-534, 2000

3. **Hollowell JG, Staehling NW, Flanders WD et al.** Serum TSH, T_4, and thyroid antibodies in the United States population (1988 to 1994): National Health and Nutrition Examination Survey (NHANES III). *J Clin Endocrinol Metab* 87: 489-499, 2002

4. **Perros P, McCrimmon RJ, Shaw G, Frier BM.** Frequency of thyroid dysfunction in diabetic patients: value of annual screening. *Diabet Med* 12: 622-627, 1995

5. **Smithson MJ.** Screening for thyroid dysfunction in a community population of diabetic patients. *Diabet Med* 15: 148-150, 1998

6. **Barker JM.** Clinical review: Type 1 diabetes-associated autoimmunity: natural history, genetic associations, and screening. *J Clin Endocrinol Metab* 91: 1210-1217, 2006

7. **Mouradian M, Abourizk N.** Diabetes mellitus and thyroid disease. *Diabetes Care* 6: 512-520. 1983

8. Hage M, Zantout MS, Azar ST. Thyroid disorders and diabetes mellitus. *J Thyroid Res* 2011: 439-463, 2011

9. Brenta G. Diabetes and thyroid disorders. *Br J Diabetes Vasc Dis* 10: 172-177, 2010

10. Bech K, Damsbo P, Eldrup E et al. β-cell function and glucose and lipid oxidation in Graves' disease. *Clin Endocrinol (Oxf)* 44: 59-66, 1996

11. Beer SF, Parr JH, Temple RC, Hales CN. The effect of thyroid disease on proinsulin and C-peptide levels. *Clin Endocrinol (Oxf)* 30: 379-383, 1989

12. Solá E, Morillas C, Garzón S, Gómez-Balaguer M, Hernández-Mijares A. Association between diabetic ketoacidosis and thyrotoxicosis. *Acta Diabetol* 39: 235-237, 2002

13. Bhattacharyya A, Wiles PG. Diabetic ketoacidosis precipitated by thyrotoxicosis. *Postgrad Med J* 75: 291-292, 1999

14. Kadiyala R, Peter R, Okosieme OE. Thyroid dysfunction in patients with diabetes: clinical implications and screening strategies. *Int J ClinPract* 64: 1130-1139, 2010

15. The Diabetes Control and Complications Trial Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. *NEJM* 329: 977-986, 1993

16. Writing Team for the Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications Research Group. Sustained effect of intensive treatment of type 1 diabetes mellitus on development and progression of diabetic nephropathy. The Epidemiology of Diabetes Interventions and Complications (EDIC) Study. *JAMA* 290: 2159-2167, 2003

17. UK Prospective Diabetes Study (UKPDS) Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). *Lancet* 352(9131): 837-853, 1998

18. UK Prospective Diabetes Study (UKPDS) Group. Effect of intensive blood-glucose control with metformin on complications in overweight patients with type 2 diabetes (UKPDS 34). *Lancet*, 352(9131): 854-865, 1998

19. American Diabetes Association. Standards of medical care in diabetes – 2013. *Diabetes Care* 36(Suppl 1): S11-S66. 2013

20. Inzucchi SE, Bergenstal RM, Buse JB et al. Management of hyperglycaemia in type 2 diabetes: a patient-centered approach. Position statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). *Diabetologia* 55: 1577-1596, 2012

21. Potenza M, Via MA, Yanagisawa RT. Excess thyroid hormone and carbohydrate metabolism. *Endocr Pract* 15: 254-262, 2009

22. Cooppan R, Kozak GP. Hyperthyroidism and diabetes mellitus. An analysis of 70 patients. *Arch Intern Med* 140: 370-373, 1980

23. Zosin I, Vlad M, Crista C, Anghel A. The evaluation of iodine intake by means of ioduria and thyroid volumetry in children from Timisoara. *Timisoara Medicala* XLI(1-2): 32-37, 1996

24. Vlad M, Tirla MA, Banica D, Milos A, Zosin I. The distribution of thyroid pathology in a region with adequate iodine intake. *Acta Endocrinologica (Buc)* IX (1, Suppl 1): 9-10, 2013

25. Chin KY, Ima-Nirwana S, Mohamed IN, Aminuddin A, Johari MH, Ngah WZ. The relationships between thyroid hormones and thyroid-stimulating hormone with lipid profile in euthyroid men. *Int J Med Sci* 11: 349-355, 2014

26. Boelaert K, Franklyn JA. Thyroid hormone in health and disease. *J Endocrinol* 187: 1-15, 2005

27. Franklyn JA, Maisonneuve P, Sheppard MC, Betteridge J, Boyle P. Mortality after the treatment of hyperthyroidism with radioactive iodine. *N Engl J Med* 338: 712-718, 1998