© **2018** ILEX PUBLISHING HOUSE, Bucharest, Roumania
http://rjdnmd.org
Rom J Diabetes Nutr Metab Dis. **25**(1):083-089
doi: 10.2478/rjdnmd-2018-0009

EVALUATION OF COGNITIVE FUNCTION IN PATIENTS WITH TYPE 2 DIABETES AND OVERT HYPOTHYROIDISM

Rucsandra Dănciulescu Miulescu [1,2,✉], ***Denisa Margină*** [1], ***Anca Ungurianu*** [1], ***Roxana Irina Roșca*** [1,3], ***Alina Nicolau*** [1,2], ***Andrada Doina Mihai*** [1,2]

[1] Carol Davila University of Medicine and Pharmacy, Bucharest
[2] "N.C.Paulescu" National Institute of Diabetes, Nutrition and Metabolic Diseases, Bucharest
[3] "C.I.Parhon" National Institute of Endocrinology, Bucharest

received: November 20, 2017 *accepted*: January 12, 2018
available online: March 15, 2018

Abstract

Background and Aims. *Previous studies report the presence of cognitive impairment in patients with overt hypothyroidism. The thyroid hormones are essential for neurological and intellectual functions. Type 2 diabetes mellitus (T2DM) subjects are exposed to higher risk of cognitive function alteration compared to nondiabetic subjects. The aim of the present study was to analyze the cognitive function of T2DM subjects with overt hypothyroidism.* ***Materials and Methods.*** *We performed an observational study between 2015-2017. A total of 12 patients (11 women and 1 men) with overt hypothyroidism and T2DM were recruited for this study. Their cognitive function was compared with that of subjects of a control group (16 patients - 12 women and 4 men with T2DM but without overt hypothyroidism). Cognitive function was evaluated using the Mini Mental State Examination (MMSE) test. Serum thyroid stimulating hormone (TSH) levels were measured by immunoradiometric assay, free thyroxine (FT4) by radioimmunoassay while fasting plasma glucose (FPG) levels were evaluated using automated devices.* ***Results.*** *There were no significant differences between the two groups in respect of age and FPG. In the study group, mean TSH and FT4 levels were 11.76±4.43 mIU/L, resepectively 0.53±0.08 ng/dL while in the control group these were 2.60±0.40 mIU/L, respectively 1.12±0.19 ng/dL ($p<0.001$). Moderate cognitive impairment was present in 3 patients of the study group (25.00%) and in 2 subjects from the control group (12.50%). Mild cognitive impairment was present in 4 patients (33.33%) of the study group and in 2 subjects from the control group (12.50%).* ***Conclusion.*** *This study showed that MMSE scores are significantly reduced in subjects with T2DM and hypothyroidism compared to subjects with T2DM without hypothyroidism ($p<0.004$). The study revealed a negative correlation between TSH and MMSE score in the study group.*

key words: *cognitive impairment, overt hypothyroidism, type 2 diabetes mellitus*

Background and Aims

Previous studies reported the presence of cognitive impairment in patients with overt hypothyroidism [1-4], being well known that thyroid hormones are essential for neurological and intellectual functions. The consequences of deficiency of thyroid hormone on cognitive

✉ 5-7 Ion Movila Street, Bucharest, District 2. Tel: 0040748134500. Fax: 004021/2105575.
corresponding author e-mail: rucsandra_m@yahoo.com

function in experimental models suggest the presence of changes in the hippocampus [5,6]. In an issue of the Neuroscience & Biobehavioral Reviews published in 2002 entitled "Thyroid hormones, brain function and cognition: a brief review", Smith JW and coauthors assert that "*thyroid hormones (THs), also regulate neural development; the central nervous system is particularly dependent on TH for normal maturation and function. Specifically, there appears to be extensive inter-reliance between TH and acetylcholine (Ach), nerve growth factor and hippocampal function"* [7].

Observational studies and experimental models that have studied the effect of hypothyroidism on cognitive and behavioral deficits found that the consequences of thyroid hormone deficiency are dependent on the severity of hypothyroidism, the duration of the defficit and the moment when the dysfunction occurs [8,9]. Hogervorst E *et al.* showed that high serum thyroid stimulating hormone (TSH) levels correlate with lower Mini Mental State Examination (MMSE) performance [10]. In a cross-sectional study, van Boxtel *et al* reported that higher TSH levels were predictive for a lower level of memory performance [11].

Patients with type 2 diabetes (T2DM) have an increased risk of cognitive alteration compared to the population that does not have this condition. Cognitive dysfunction in patients with T2DM may be associated with vascular dysfunction, and direct „toxic" effects of high blood glucose on brain neurons [12].

The aim of the present study was to analyze the cognitive function of T2DM subjects with overt hypothyroidism.

Materials and Methods

We performed an observational study based on T2DM patients admitted in the inpatient diabetes wards of „N. C. Paulescu" National Institute of Diabetes, Nutrition and Metabolic Diseases, Bucharest between 2015 and 2017. The study group included 12 patients (11 women and 1 men) with overt hypothyroidism and T2DM. The control group included 16 patients (12 women and 4 men) with T2DM but without overt hypothyroidism. *Overt hypothyroidism* was defined based on the presence of high serum TSH level with concomitant low free thyroxine (FT4) concentration. Serum TSH was measured by immunoradiometric assay, within the reference range of normal subjects: 0.4-4.5 mIU/L and FT4 were measured by radioimmunoassay (reference range 0.7-1.8 ng/dL). FPG levels were evaluated using automatic devices.

The cognitive function was evaluated with the help of the MMSE test, an examination that was developed and published in 1975 to reflect the cognitive status [13]. A MMSE score $\geq$ 24 points proves a normal cognitive function. Mild cognitive impairment it is characterized by a score between 19-23 points, moderate cognitive impairment 10-18 points and severe cognitive dysfunction $\leq$ 9 points [13].

All study subjects signed an informed consent prior to any study procedure while the study protocol was reviewed and approved by the local ethics committee.

Statistical analysis All results are presented as mean±SD. The obtained results were compared between groups using the t Student Test and values <0.05 were considered significant. For the evaluation of correlations between variables we calculated Pearson's correlation coefficients. All results were analyzed using the SPSS® (Statistical Package for Social Sciences Software) package, version 15.

Results

Patients were aged between 58 and 77 years (mean age 64.92±5.84 years in diabetic patients with overt hypothyroidism and 61.88±3.12 years in patients without overt hypothyroidism). There were no significant differences between the two study groups in respect to age and FPG (as shown in Figures 1 and 2).

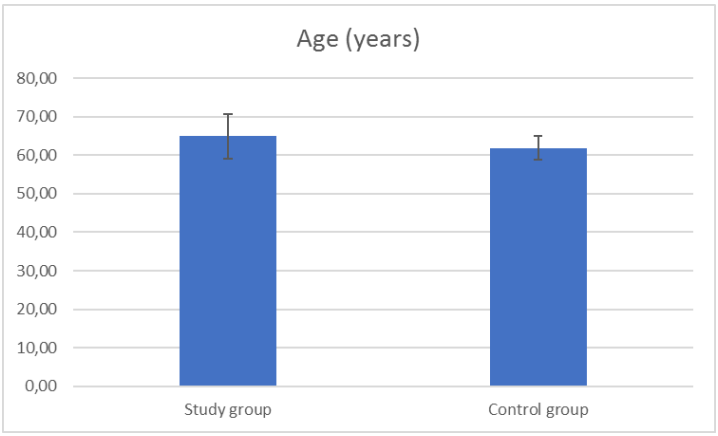

Figure 1. *Mean age in study and control group.*

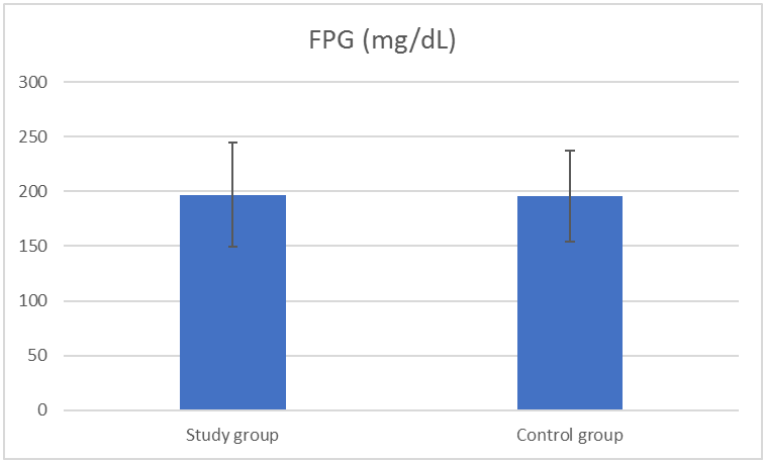

Figure 2. *Mean FPG in study and control group.*

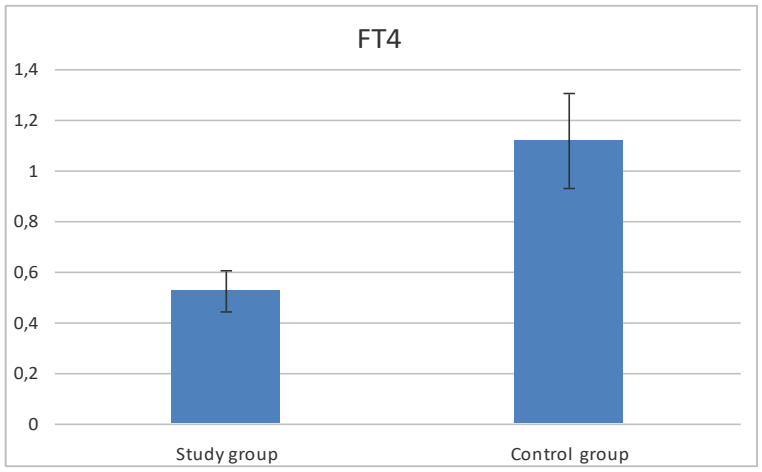

Figure 3. *FT4 in study and control group.*

Higher titers of anti–thyroid peroxidase antibodies were present in 5 patients of the study group (41.66%). In the study group mean TSH and FT4 levels were 11.76±4.43 mIU/L, respectively 0.53±0.08 ng/dL while in control group these were 2.60±0.40 mIU/L, respectively 1.12±0.19 ng/dL (p<0.001). TSH and FT4 values for the study and control groups are presented in Figures 3 and 4.

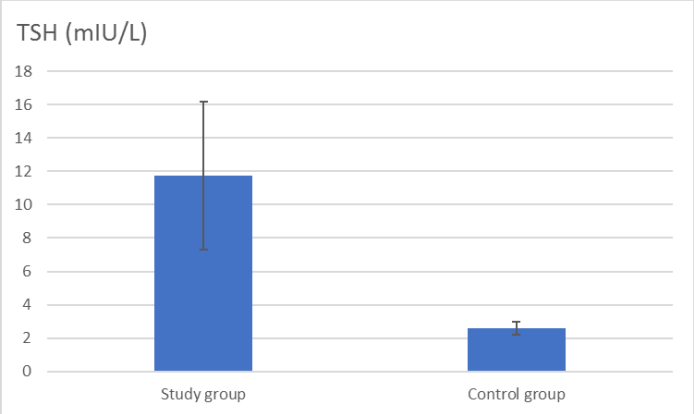

Figure 4. *The result of TSH in study group and control group.*

Table 1. Characteristics of patients from the study and control group.

	Study group	Control group	P
Age (years)	64.92±5.84	61.88±3.12	NS
FPG (md/dL)	196.83±47.78	196.06±41.63	NS
TSH (mIU/L)	11.76±4.43	2.60±0.40	<0.001
FT4 (ng/dL)	0.53±0.08	1.12±0.19	<0.001
MMSE (points)	21.17±4.14	24.50±3.62	0.04

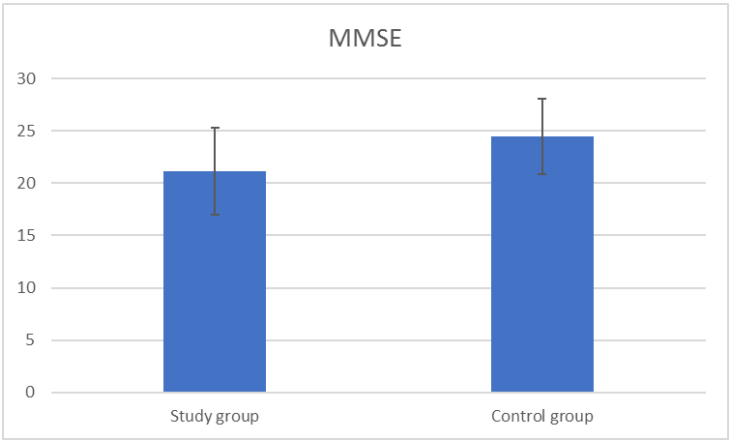

Figure 5. *MMSE in study group and control group.*

A moderate cognitive impairment was present in 3 patients of the study group (25.00%) and in 2 subjects of the control group (12.50%). A mild cognitive impairment was present in 4 patients (33.33%) of the study group and in 2 subjects of the control group (12.50%).

The main differences between the study and control group are presented in Table 1.

We present the results of the MMSE testing for the two study groups in Figure 5.

Finally, our study revealed a negative correlation between TSH levels and MMSE score in the study group as shown in Figure 6.

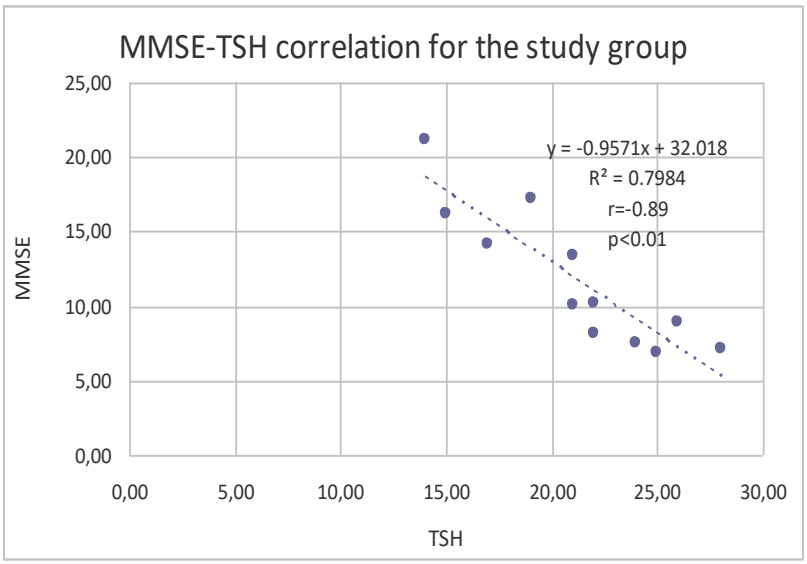

Figure 6. *Correlation between TSH and MMSE score in the study group.*

Discussions

The link between deficienncy of thyroid hormones and cognitive function has been assessed in several studies. Thus, in 2008 Begin ME *et al* published in *Current Gerontology and Geriatrics Research* a review about "Thyroid Function and Cognition during Aging". The authors mention that "*Common cognitive deficits observed in middle-aged clinical hypothyroid patients include diminished general cognition, attention, learning, memory, and psychomotor speed. However, language comprehension and possibly sustained auditory attention are less impaired than other cognitive functions in clinical hypothyroidism*" [14].

The present study showed that MMSE is significantly decreased in subjects with T2DM and overt hypothyroidism compared to the control group ($p<0.004$). These results are consistent with those of previously published studies. Thus, the results of a study in wich were included 54 hypothyroid patients showed that hypothyroid patients have significantly lower scores on the MMES as compared to control group (30 euthyroid subjects) [15].

Cognitive function of elderly patients diagnosed with subclinical hypothyroidism was investigated also by Bajaj S *et al* in a cross-sectional, case-control study. In this study were included 103 patients with subclinical hypothyroidism compared with 103 age, sex and education-matched healthy subjects. The study showed that the frequency of cognitive deficit in patients with subclinical hypothyroidism was significantly higher compared to controls [16].

Our results regarding correlation bewteen TSH and cognitive function are also similar with those from other studies. In 1998 Wahlin A *et al* published in *Journals of Gerontology* a study about the relationship between T4 / TSH and cognitive function in subjects of very old age. In this study were included 200 participants. The authors mention that "*Results indicated that T4 was unrelated to performance. However, TSH was positively related to episodic memory performance, and the effects were independent of the influence of age, level of education, and depressive mood symptoms The finding that TSH, in contrast to T4, was related to cognitive performance may reflect the fact that TSH is the major modulator of thyroid functioning"* [17]. Another study published in 2004 in *Psychoneuroendocrinology* included 120 subjects aged between 49 and 71 years and

showed *"a negative association between TSH and memory function was apparent: higher levels of TSH predicted lower levels of memory performance"* [11].

Begin ME *et al* reported in a review published in 2008 that *"although thyroid hormones may have an impact on a variety of cognitive functions, only a link to certain memory functions has been so far highlighted. Differences in results may be due to differences in sample selection, age ranges, choice of cognitive tests, and to higher TSH and cognitive variability with increasing age and limited number of thyroid function indices"* [14]. Finally, Bajaj S *et al* and Jorde et al reported that serum TSH correlates negatively with the cognitive function [16,18].

This study has some limitations. First, this was an obsevational study with a small number of patients and statistical significance of obtained data should be interpreted with caution. The second limitation is that only a single thyroid hormone determination was used to diagnose overt hypothyroidism. Future studies including higher number of patients are required to confirm the link between thyroid function and cognitive dysfunction.

Conclusion

This study showed that MMSE scores are significantly reduced in T2DM subjects with overt hypothyroidism compared to control T2DM patients ($p<0.004$). The study revealed a negative correlation between TSH and MMSE score in the study group. Future studies are needed to confirm the role of thyroid hormone deficiency on cognitive function.

REFERENCES

1. **Ceresini G, Lauretani F, Maggio M et al.** Thyroid function abnormalities and cognitive impairment in elderly people: results of the Invecchiare in Chianti study. *J Am Geriatr Soc* 57: 89–93, 2009.

2. **Correia N, Mullally S, Cooke G et al.** Evidence for a specific defect in hippocampal memory in overt and subclinical hypothyroidism. *J Clin Endocrinol Metab*, 94: 3789–3797, 2009.

3. **Quinlan P, Nordlund A, Lind K, Gustafson D, Edman A, Wallin A.** Thyroid hormones are associated with poorer cognition in mild cognitive impairment. *Dement Geriatr Cogn Disord* 30: 205–211, 2010.

4. **Gussekloo J, Van Exel E, De Craen AJ, Meinders AE, Frölich M, Westendorp RG**. Thyroid status, disability and cognitive function, and survival in old age. *JAMA* 292: 2591–2599, 2004.

5. **Gilbert ME, Sui L**. Dose-dependent reductions in spatial learning and synaptic function in the dentate gyrus of adult rats following developmental thyroid hormone insufficiency. *Brain Res* 1069: 10–22, 2006.

6. **Goldey ES, Kehn LS, Rehnberg GL, Crofton KM**. Effects of developmental hypothyroidism on auditory and motor function in the rat. *Toxicol Appl Pharmacol* 135: 67–76, 1995.

7. **Smith JW, Evans AT, Costall B, Smythe JW**. Thyroid hormones, brain function and cognition: a brief review. *Neurosci Biobehav Rev* 26: 45–60, 2002.

8. **Morreale de Escobar, G, Obregon MJ, del Rey FE.** Maternal thyroid hormones early in pregnancy and fetal brain development. *Best Pract Res Clin Endocrinol Metab* 18: 225–248, 2004.

9. **Zoeller RT, Rovet J.** Timing of thyroid hormone action in the developing brain: clinical observations and experimental findings. *J Neuroendocrinol* 16: 809–818, 2004.

10. **Hogervorst E, Huppert F, Matthews FE, Brayne C.** Thyroid function and cognitive decline in the MRC funded cognitive function and ageing study. *Psychoneuroendocrinology* 33: 1013–1022, 2008.

11. **van Boxtel MPJ, Menheere PPCA, Bekers O, Hogervorst E, Jolles J.** Thyroid function, depressed mood, and cognitive performance in older individuals: the Maastricht aging study. *Psychoneuroendocrinology* 29: 891–898, 2004.

12. Umegaki H. Type 2 diabetes as a risk factor for cognitive impairment: current insights. *Clin Interv Aging* 9: 1011–1019, 2014.

13. Folstein MF, Folstein SE, McHugh PR. Mini-mental state. A practical method for grading the cognitive state of patients for the clinician. *J Psychiatr Res* 12: 189–198, 1975.

14. Begin ME, Langlois MF, Lorrain D, Cunnane SC. Thyroid Function and cognition during aging. Curr Gerontol Geriatr Res 2008: 474868, 2008.

15. Osterweil D, Syndulko K, Cohen NS et al. Cognitive function in non-demented older adults with hypothyroidism. *JAGS* 40 :325-335,1992.

16. Bajaj S, Sachan S, Mirsa V, Varma A, Saxena P. Cognitive function in subclinical hypothyroidism in elderly. *Indian J Endocrinol Metab* 18(6): 811–814, 2014.

17. Wahlin Å, Wahlin T-BR, Small BJ, Bäckman L. Influences of thyroid stimulating hormone on cognitive functioning in very old age. *Journals of Gerontology. Series B* 53: P234–P239, 1998.

18. Jorde R, Waterloo K, Storhaug H, Nyrnes A, Sundsfjord J, Jenssen TG. Neuropsychological function and symptoms in subjects with subclinical hypothyroidism and the effect of thyroxine treatment. *J Clin Endocrinol Metab* 91: 145–153, 2006.