Neuroendocrinology Letters Volume 31 No. 3 2010
Reprinted from: Act Nerv Super Rediviva 2010; 52(1): 77–83

Cognitive Disorders in Type 2 Diabetic Patients with Recognized Depression

Anna Janocha [1], Marek Bolanowski [2], Witold Pilecki [3], Krzysztof Małyszczak [4], Ewa Salomon [1], Wojciech Woźniak [1], Robert Skalik [1], Anna Tumińska [1], Dariusz Kałka [3], Małgorzata Sobieszczańska [3]

1 Department of Physiology, Wroclaw Medical University, Poland;
2 Department of Endocrinology, Diabetology and Isotope Therapy, Wroclaw Medical University, Wroclaw, Poland;
3 Department of Pathophysiology, Wroclaw Medical University, Wroclaw, Poland;
4 Department of Psychiatry, Wroclaw Medical University, Wroclaw, Poland

Correspondence to: Anna Janocha, M.D., Ph.D., Department of Physiology, Wroclaw Medical University, Chałubińskiego str. 10, 50-368 Wroclaw, Poland.
TEL. +48 71 784 14 26; FAX +48 71 784 00 92;
E-MAIL: ajanocha@fizjo.am.wroc.pl

Submitted: 2010-01-12 Accepted: 2010-02-05 Published online: 2010-06-30

Key words: **diabetes mellitus type 2; depressive symptoms; cognitive disorders; sensomotor skills**

Neuroendocrinol Lett 2010; **31**(3):399–405 **PMID:** 20588250 NEL310310A20

Abstract

OBJECTIVES: The most important factors in the pathogenesis of cognitive disorders in diabetes mellitus (DM) are metabolic changes directly caused by hyperglycemia. Impairment of cognitive function is accompanied by a decrease in cerebral insulin. Insulin improves cognitive processes, including somatosensoric cognitive functions. Cognitive disorders are especially pronounced if diabetic patients suffer also from depression.

MATERIAL AND METHODS: The evaluation of cognitive functions, especially sensomotoric skills were obtained from three study groups (aged 37-52 years): 30 healthy subjects, 40 diabetic patients with clinically documented depression and 30 depressive patients without DM. The sensomotoric skills were carried out using a SPS-2001E apparatus – a computer working stress simulator. The examination with Beck Depression Inventory (BDI) were also performed in all the investigated persons.

RESULTS: Sensomotoric skills investigation revealed slight cognitive disorders in the early stages DM (subgroup IA) and its intensification according to increasing BDI scores and HbA1c blood concentration (from subgroup IA to IC). Intensification of sensomotoric cognitive disorders was significantly higher ($p<0.001$) in the depressive patients with DM (group I), than in these without DM (group III).

CONCLUSIONS: The obtained results suggest that coincidence of aggravating factors, such as depression and metabolic disorders in DM, may cause mutual interactions leading to premature and more intense cognitive impairment. The method proposed by the authors may serve as a screening examination in early diagnosis of CNS disorders reflected by somatosensoric cognitive disorders. The presented work indicates importance of sensomotoric skills investigation for the early diagnosis of the nervous system damage related to DM.

ORIGINAL ARTICLE

Abbreviations:
DM – diabetes mellitus;
CNS – central nervous system;
BDI – Beck depression inventory;
HbA1c – glycated hemoglobin
MDD – major depressive disorder

INTRODUCTION

The effect of diabetes mellitus (DM) on development of multi-organ complications is a well-known fact, which has been widely discussed in the literature. The most important pathogenetic factors mentioned by authors include absolute or relative hypoinsulinemia with subsequent hyperglycaemia. Very well-known diabetes complications include nervous system disorders, especially impairment of peripheral nerve and autonomic nerve function. Little is known, yet, about the effect of DM on the central nervous system (CNS) with its cognitive functions. These functions are necessary to gain knowledge of the surrounding world, as well as acquire and analyze information, which in consequence allow making correct decisions and functioning in every-day life. An important role among cognitive functions is played by sensomotoric skills, especially visual-motor coordination, concentration, attention switching ability and psychomotor speed.

An important role in development of cognitive disorders is played by decreased insulin production, which is observed in type 2 diabetes mellitus, or receptor resistance to insulin in its target tissues. Central insulin receptors are mainly localized in the hippocampus, olfactory bulbs and hypothalamus, and insulin reaching the brain through the blood-brain barrier may influence the quality of cognitive functions. It is known that cognitive function impairment, which is closely related to the aging process, is accompanied by a decrease in cerebral insulin. Similar changes also occur in the Alzheimer's disease. On the other hand, the most recent findings indicate that cerebral insulin improves cognitive processes and memory, especially hippocampus-dependent declarative memory (Stockhorst et al 2004; Benedict et al 2007; Laron 2009).

As a part of the limbic system, hippocampus takes part in neuroendocrine responses to emotional stressors. Under theses stressors, the release of acetylcholine in the hippocampus increases, which coincides with the elevation of plasma glucose (Adeli-Rankouchi et al 2005). Emotional stressors, like depression, activate the other part of limbic areas – amygdala. Activation of amygdala caused chronic elevation in cortisol levels, which is known as a stress hormone. A high level of cortisol leads to tissue insulin resistance, reduces glucose uptake by the muscles and elevation of plasma glucose (Takahashi et al 2005; Janocha et al 2009). The above-mentioned facts prove that emotive stimuli may affect the progress of somatic diseases, such as DM. Similarly, a somatic disease may affect the quality of mental functions, including cognitive ones.

The authors of the present study have attempted to evaluate cognitive functions, especially sensomotoric skills in subjects with type 2 DM. This study examined also the association of type 2 diabetes, depression and cognitive disorders.

MATERIAL AND METHODS

Subjects

A group I of 40 diabetic patients (25 females and 15 males), recruited from Wrocław Center for Neurosis Treatment, was enrolled in the study. The examined group was ranging in age from 38 to 53 years, with the mean age of 44.6 ± 4.37 years. A disease history was obtained from all patients, and then each patient underwent a detailed clinical examination and basic laboratory parameters assessment. From the clinical point of view, all these patients had DM type 2 detected, and most of them showed the apparent, reliably documented symptoms and signs of depression varying in degree of severity. Diabetic patients were under treatment with oral hypoglycemic agents or with add of insulin injections (once daily); with the mean DM duration of 6.45 ± 4.02 years. The results of the investigations in the patients group were referred to the outcomes obtained from the control group (group II) comprising 30 healthy, age- and sex-matched volunteers (age range: 38-51 years; mean age 44.7 ± 4.26 years; 18 females, 12 males) with no history of the previous episodes of depression.

Subjects with recognized depression, but without diabetes mellitus (group III) also constituted specific reference for group I, comprising 30 persons, age- and sex-matched volunteers (age range: 37-52 years; mean age 44.4 ± 4.96 years; 19 females, 11 males).

Methods

The studies on sensomotoric skills presented in this paper were conducted at the Psychomotoric Laboratory of the Department of Physiology at the Wrocław Medical University, with the use of advanced MSS-2001E system developed by GPE Psychotronics and EIEWIN (Poland). The system includes a research keyboard and a control panel. A two-dimensional button system on the keyboard (with an emitter of light impulses) limits the field of view of the patient, which increases his concentration. The control panel allows selection of an adequate program, depending on the frequency of impulse exposure per minute (60, 75, 93, 107, 125 impulses) and on the duration of one sequence (30, 60, 90, 120 seconds). The system allows to examine visual-motor coordination with concurrent time registration for each response and to identify the average response time, coordination skills expressed as percentages and the number of received and incorrect answers. The patient reacts to each light impulse exposed on the keyboard by pushing an appropriate button. After each exposure, the control panel screen displays the response

characteristics, e.g. correct, delayed, incorrect, no response and response time expressed in milliseconds. Laboratory standards were selected after examining 200 healthy subjects and they included coordination skills. The reason for selection of this particular parameter is that it is expressed as percentages, which is important if the examination is performed at various exposure frequencies per minute. The following standards for coordination skills were determined: 86-100% - very good result; 71-85% - good result; 55-70% - satisfactory result; <55% - unsatisfactory result.

The present study used examinations performed at various frequencies of impulse exposure (60, 75, 93, 107 and 125 per min) and constant duration time of one sequence (60 s).

The self-assessment charts, like Beck Depression Inventory (BDI) used in the present study, are considered to be of great usefulness in establishing a diagnosis of depression. The examined subject is requested to complete the questionnaire which consists of 22 issues; for each of the questions you can choose only one answer (yielding 0-3 scores). It is assumed that an outcome of the whole test exceeding 12 scores indicates depression.

Also a measurement of glycated hemoglobin (HbA1c), as a most reliable index of diabetic control, was performed.

Statistical analysis

Standard statistical Student t-test was applied for comparison of the two variables. The values are presented as the mean ± SD, and a level of statistical significance was set at $p<0.05$. Non-parametric data was given as the absolute numbers or percentages.

RESULTS

Diabetic patients were divided into three subgroups (IA, IB, IC) according to their last glycated hemoglobin and BDI scores. Depressive patients were divided into two subgroups (IIIA and IIIB) according to their BDI scores. Characteristics of these subgroups and the control group are compiled in Table 1 and Table 2.

Subgroup IA had the lowest mean age of subjects, and it was significantly higher ($p<0.001$) in subsequent subgroups, reaching the highest value in the subgroup IC. With reference to the control group, only subgroup IB showed no statistical difference. The remaining groups revealed differences that were statistically significant ($p<0.001$). No statistically significant differences in the mean age were observed between group II and group III subgroups.

Mean value of BDI and percentage contribution of HbA1c showed a clear tendency to increase gradually within the subgroups IA-IC. The exact analysis of the BDI outcomes in these subgroups let us diagnose a depression in subgroups IB and IC, only. These results were referred to the control group, where BDI scores and HbA1c were: 6.5 ± 1.07 scores and 4.6 ± 0.48%, respectively. Difference between the three patient subgroups and control group was statistically significant ($p<0.001$). The results of the BDI and HbA1c obtained in the control group let us exclude a diagnosis of depression and DM. None of the control subjects reported any depressive episode also in the past. In the group III,

Tab. 1. Characteristics of the diabetic patients from the subgroups IA-IC.

Groups	Group I (N = 40)		
	Subgroup IA (N = 17)	**Subgroup IB (N = 13)**	**Subgroup IC (N = 10)**
Mean age	40.47 ± 1.73 years	45.69 ± 2.21 years	50.2 ± 1.54 years
DM duration	1 – 5 years mean 2.58 ± 1.57	>5 – 10 years mean 7.38 ± 1.54	>10 years mean 11.8 ± 1.2
BDI	8.53 ± 1.01 scores	16.8 ± 0.92 scores	27.2 ± 1.56 scores
Depressive symptoms	None	Single moderate depressive episodes	Recurrent depressive episodes incl. MDD
HbA1c	6.6 ± 0.33%	8.1 ± 0.6%	12.9 ± 0.71%

Tab. 2. Characteristics of the depressive patients from the subgroups IIIA and IIIB and the control group II.

Groups	Group III (N = 30)		Group II (N=30)
	Subgroup IIIA (N = 16)	**Subgroup IIIB (N = 14)**	
Mean age	43.99 ± 3.71 years	44.21 ± 2.95 years	44.7 ± 4.26 years
DM duration	Healthy	Healthy	Healthy
BDI	16.2 ± 1.03 scores	27.8 ± 1.82 scores	6.5 ± 1.07 scores
Depressive symptoms	Single moderate depressive episodes	Recurrent depressive episodes incl. MDD	None
HbA1c	4.7 ± 1.26%	4.9 ± 1.93%	4.6 ± 0.48%

Tab. 3. Results of sensomotoric skills of the diabetic patients in the subgroups IA-IC and in the control group II using MSS-2001E apparatus. Duration of one sequence – 60 s.

Frequency of impulse exposure per min	Subgroup IA	Subgroup IB	Subgroup IC	Group II
Reaction time [ms]				
60/min	587.23 ± 68.25	694.3 ± 51.04	795.1 ± 33.38	375.73 ± 45.36
75/min	664.23 ± 45.18	751.3 ± 18.23	Deny	404.13 ± 28.05
93/min	699.41 ± 57.36	Deny	Deny	414.9 ± 35.2
107/min	712.47 ± 51.38	Deny	Deny	422.7 ± 37.38
125/min	Deny	Deny	Deny	431.8 ± 39.72
Sensomotoric skills [%]				
60/min	81.66 ± 9.63	63.16 ± 4.38	42.07 ± 3.33	100 ± 0
75/min	79.92 ± 7.01	60.33 ± 5.61	Deny	97.8 ± 6.12
93/min	77.14 ± 8.33	Deny	Deny	96.66 ± 5.88
107/min	72.42 ± 6.13	Deny	Deny	91.76 ± 5.23
125/min	Deny	Deny	Deny	90.21 ±8.75
Number of wrong answers				
60/min	11.05 ± 1.6	22.53 ± 3.09	34.77 ± 2.05	0 ± 0
75/min	15.07 ± 1.34	29.07 ± 2.78	Deny	1.12 ± 0.8
93/min	21.23 ± 2.25	Deny	Deny	2.66 ± 0.95
107/min	29.52 ± 2.98	Deny	Deny	8.5 ± 4.96
125/min	Deny	Deny	Deny	12.21 ± 2.87
Number of correct answers				
60/min	48.99 ± 6.35	37.89 ± 6.12	25.24 ± 2.42	60 ± 0
75/min	59.94 ± 4.45	45.24 ± 7.5	Deny	73.35 ± 5.34
93/min	71.74 ± 5.27	Deny	Deny	89.89 ± 3.88
107/min	77.48 ± 4.94	Deny	Deny	98.18 ± 3.22
125/min	Deny	Deny	Deny	112.76 ± 5.21

the results of the HbA1c let us exclude a diagnosis of DM, but analysis of the BDI outcomes let us diagnose a depression.

Like other parameters, the mean DM duration had a similar growing tendency in subsequent groups IA-IC and the difference between the subgroups was also statistically significant ($p<0.001$). However, this parameter could not be assessed with reference to group II and III, since neither of them comprised patients with recognized DM.

Table 3 shows the results obtained in the subgroups of group I and in group II with the use of an instrument measuring sensomotoric skills.

The results obtained in group II were assumed as the standard results, since they were within the range of very good values and were significantly higher ($p<0.001$) than analogical results obtained in subgroups IA-IC.

In group I, subjects from the subgroup IA performed the examination at almost all frequencies of impulse exposure that were performed by group II subjects, except for the frequency of 125 per minute. The results obtained in the subgroup IA were within the range of values considered as good and were significantly different ($p<0.001$) with reference to the remaining groups. Subjects from the subgroup IB performed the test at two first emission frequencies (60 and 75 per min), and subjects from the subgroup IC at the frequency of 60 per min, only. They made no attempt and refused to perform the task at the remaining frequencies. The results obtained in subgroup IB were considered satisfactory with reference to the standard and those obtained in subgroup IC were unsatisfactory. The differences between these subgroups were statistically significant ($p<0.001$). In these circumstances, the comparison of all subgroups of group I and the control group could only be conducted at the emission frequency of 60 per min. The results obtained under such circumstances showed statistically significant ($p<0.001$) differences among subgroups IA-IC. A similar significance was also revealed with reference to the control group.

Fig. 1 and Fig. 2 show the comparison of coordination skills in patients from group I and III with recognized depression. Only group I patients were additionally diagnosed with diabetes mellitus.

Fig. 1 compares subgroups IB and IIIA having similar intensity of depression symptoms and similar BDI (IB – BDI 16.8 ± 0.92 scores; IIIA – BDI 16.2 ± 1.03 scores). Subjects from both subgroups performed the test on the MSS-2001E system only at two frequencies of impulse emission, i.e. 60 and 75 per min. The results with regard to coordination skills were significantly

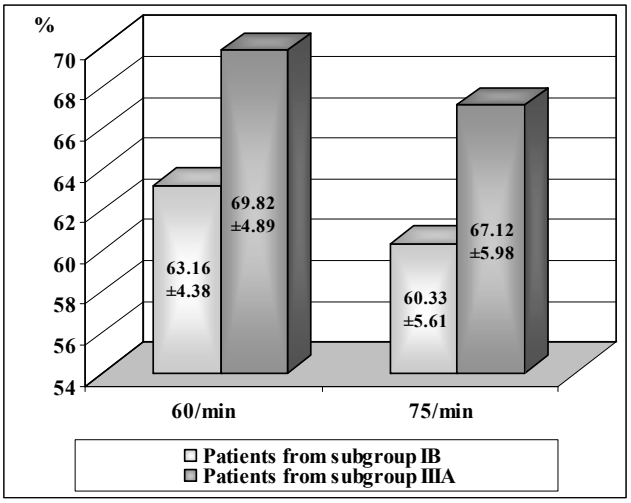

Fig. 1. Comparison of coordination skills in the patients with recognized depression in subgroups IB i IIIA with similar BDI (about 16 scores).

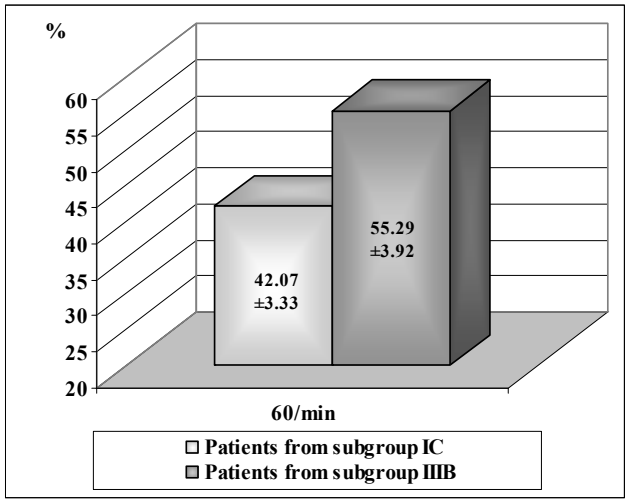

Fig. 2. Comparison of coordination skills in the patients with recognized depression in subgroups IC i IIIB with similar BDI (about 27 scores).

lower ($p<0.001$) in group IB, than analogical results obtained in group IIIA.

Fig. 2 compares subjects from subgroups IC and IIIB, whose BDI was IC – 27.2 ± 1.56 scores and IIIB – 27.8 ± 1.82 scores, respectively. Subjects from both these subgroups attempted to perform the test only at the lowest frequency of impulse emission, i.e. 60 per min. Similarly to the previous groups, the coordination skills results were significantly lower ($p<0.001$) in subjects from group I (subgroup IC) than in subjects from group III (subgroup IIIA). It should be noticed that only the subjects from subgroup IC obtained results that were considered unsatisfactory with reference to the standard.

DISCUSSION

Recent findings more and more frequently emphasize the correlation between endocrinological disorders and cognitive disorders (Ruis et al 2009; Roriz-Filho et al 2009; Izydorczyk & Rybicka-Klimczyk 2009). These disorders are especially pronounced in diabetic patients suffering also from depression. Concurrence of these two diseases is quite frequent, since depression in diabetic patients occurs more often than in the general population and worsens the prognosis of diabetic patients (Collins et al 2009; Janocha et al 2009).

The analysis of results obtained in the present study shows that slight cognitive function impairment occurs even in the early stages of diabetes mellitus, as was the case in subgroup IA, where the mean DM duration was 2.58 ± 1,57 years (Table 3). Sensomotoric coordination was lowered in this subgroup with regard to all the examined parameters, i.e. average reaction time, coordination skills and the number of received and incorrect answers. The obtained results were significantly different ($p<0.001$) from those obtained in group II. Moreover, subjects from subgroup IA refused to perform the task at the impulse emission frequency of 125 per min because it was too fast and they did not manage to respond, whereas subjects from group II managed to perform the task without any difficulties. The most useful parameter for the comparison of cognitive functions at different frequencies of impulse emission per minute was the coordination skills expressed as percentages. Although this parameter was within the range of values considered as good in subgroup IA, it was significantly lower ($p<0.001$) at all frequencies of stimulus emission, in comparison with group II. Moreover, a gradual decrease in coordination skills was observed in subgroup IA with increased frequency of impulse emission. A similar phenomenon was also observed in group II (Table 3). The evaluation of cognitive functions in subgroup IA was very important, since its members did not fulfil the criteria of depression (Table 1), which means that the causes of cognitive function impairment may be related mainly to DM. Ruis et al. (2009) report cases of slight cognitive function impairment even in the early stage of type 2 DM. They also emphasize the patient history of a macrovascular disease and smoking, which they consider to be significant risk factors for some early decrements.

In the remaining two subgroups of group I, a further decrease in sensomotoric skills was observed with regard to all parameters (Table 3). The results obtained in subgroup IB were significantly lower ($p<0.001$) than analogical results obtained in subgroup IA and group II. The strongest cognitive disorders occurred in subgroup IC, whose results were significantly different ($p<0.001$) from the remaining subgroups of group I and from group II (Table 3). Subjects from subgroup IB

performed the test only at two lowest impulse emission frequencies (60 and 75 per min), and subjects from subgroup IC only at the frequency of 60 per min. The percentage of coordination skills obtained in subgroup IB was within the range of values considered as satisfactory and in subgroup IC within the range of values considered as unsatisfactory. The difference between subgroup IA and subgroups IB and IC was that the subjects of subgroups IB and IC suffered from depression, apart from the main diseases, i.e. diabetes mellitus. These results suggest that depression should be considered as another significant risk factor for cognitive function impairment. Some authors had noticed that depression had a negative influence on the glycaemia self-control quality in diabetic patients (Janocha et al 2009), which is also confirmed by the present studies. A characteristic feature of all three examined subgroups was an increasing DM duration and unfavourable increase in HbA1c concentration, from IA to IC, which translated to cognitive function impairment (Table 1). Both these increases, which were significantly different between subgroups ($p<0.001$), may be treated as other risk factors for cognitive disorders. Stockhorst et al. (2004) also drew attention to progressing cognitive function impairment in diabetics, together with a decrease in cerebral insulin, which results from worse diabetes self-control. According to Roriz-Filho et al. (2009) chronic hyperglycaemia may accelerate the process of cerebral aging due to widespread brain microangiopathy. Diabetes subjects are more prone to develop extense and earlier than usual leukoaraiosis and consequently they are at increased risk for cognitive impairment and dementia. Additionally, Laron et al. (2009) noticed improvement in cognitive functions following insulin administration, especially via nose-to-brain pathway, which is a quicker system of insulin delivery to the brain than the traditional one. Additionally, the localization of insulin receptors in the olfactory bulb makes insulin interesting for the nose-to-brain pathway. Nowadays, there are great expectations regarding the use of intranasal insulin in the treatment of cognitive disorders, not only in DM, but also in conditions related to the aging process, including Alzheimer's disease.

Further analysis of the results contained in Table 1, leads to the conclusion that age of diabetic subjects is another risk factor for cognitive disorders. It should be noticed that the average age of subjects was increasing in subsequent groups IA-IC and differences between the subgroups were statistically significant ($p<0.001$). Members of subgroup IC were the oldest ones, with the mean age of 50.2 ± 1.54 years. Yet, this is not the age of intensified dementia processes related to aging. Nevertheless, poor glycaemia control and the presence of additional aggravating factors, such as depression or DM mean duration may cause mutual interactions leading to premature cognitive impairment. Therefore, the cognitive function impairment increasing in subsequent groups should be considered as a resultant of all the risk factors, including the average age of the subjects. The other risk factor is obesity, thus physical activity markedly improved the patient's condition and reduced body fat. After weight loss DM patients showed better diabetes control and decrease in insulin resistance (Szabó et al 2009). According to Awad et al. (2004), type 2 DM with optimal glycaemic control has little influence on cognitive functions in subjects below 70 years of age. However, in older subjects (of 70 years or more), diabetes-related metabolic disorders are associated with other dementia processes, such as vascular disease and Alzheimer's disease, which may result in acceleration of cognitive disorders.

In order to emphasize the role of type 2 DM in development of cognitive disorders, a comparison of coordination skills between group I and III was performed. Subjects from group III constituted a specific reference group, since none of them was diagnosed with DM, whereas all of them were diagnosed with depression (Table 2) and significant decrease ($p<0.001$) in coordination skills as compared to group II. According to BDI scores, the group III was divided into subgroups IIIA and IIIB, equivalent to subgroups IB and IC. The comparison of subgroups IB and IIIA (Fig. 1) shows that despite a similar BDI value amounting to 16.8 ± 0.92 scores (IB) and 16.2 ± 1.03 scores (IIIA), coordination skills results were significantly higher ($p<0.001$) in subgroup IIIA than in subgroup IB. Similar conclusions were arrived at after comparing subgroups IC and IIIB (Fig. 2), where coordination skills were significantly higher ($p<0.001$) in subgroup IIIB than IC. The BDI values did not reveal significant differences between these subgroups and were 27.2 ± 1.56 scores (IC) and 27.8 ± 1.82 scores (IIIB). It should also be noticed that only the coordination skills results obtained in subgroup IC were below 55%, which means that were within the range of unsatisfactory values (Fig. 2). The comparisons shown on both figures clearly show the association between metabolic disorders in type 2 DM and intensification of cognitive disorders.

Authors of this paper emphasized often the importance of correctly conducted glycaemic control. However, they would like to add that a very intense therapy may also be dangerous, since hypoglycaemia may have consequences that are similarly dangerous to those resulting from hyperglycaemia. Intensive therapy can prevent or delay the development of long-term complications associated with DM, but hypoglycaemia also resulting in cognitive failure. Hypoglycaemia that may preferentially harm neurons in the hippocampus, is a potential danger for the brain cognitive function (Akyol et al 2003).

The results presented in this paper clearly show that concurrence of type 2 DM and depression may cause mutual interactions leading to premature cognitive impairment that are more intense than in these two conditions occurring separately. On the other hand, the method proposed by the authors is simple, cheap and

easily available, so it may serve as a screening examination in early diagnosis of CNS disorders, which are reflected in somatosensoric cognitive disorders. This work indicate also importance of sensomotoric skills investigation for the early diagnosis of the nervous system damage related to DM.

Emotive disorders, like depression, may have an influence on development and progress of a somatic diseases through increased insulin resistance, gluconeogenesis, increased level of proinflammatory cytokines (IL-1 and TNF-α) and activation of pituitary-adrenal axis with the sympathetic nervous system. On the other hand, stress induced by hyperglycaemia causes a further increase in proinflammatory cytokines and stress hormone, thus contributing to a negative effect on the progress of the primary diseases and on the quality of mental functions, including cognitive functions (Dungan et al 2009; Baranowska-Bik et al 2009).

In conclusion, it should be emphasised that human being constitutes psychosomatic unity. This fact must never be neglected in any diagnostic and therapeutic activities.

REFERENCES

5 Adeli-Rankouchi S, Umegaki H, Zhu W, Suzuki Y, Kurotani-Ohara S, Ieda S, et al (2005). The entorhinal cortex regulates blood glucose level in response to microinjection of neostigmine into the hippocampus. *Neuroendocrinol Lett*. **26**(3): 225-230.

6 Akyol A, Kiylioglu N, Bolukbasi O, Guney E, Yurekli Y (2003). Repeated hypoglycemia and cognitive decline. A case report. *Neuroendocrinol Lett*. **24**(1-2): 54-56.

7 Awad N, Gagnon M, Messier C (2004). The relationship between impaired glucose tolerance, type 2 diabetes, and cognitive function. *J Clin Exp Neuropsychol*. **26**(8): 1044-1080.

8 Benedict C, Hallschmid M, Schultes B, Born J, Kern W (2007). Intranasal insulin to improve memory function in humans. *Neuroendocrinology*. **86**(2): 136-142.

9 Baranowska-Bik A, Bik W, Wolinska-Witort E, Martynska L, Chmielowska M, Barcikowska M et al (2008). Plasma beta amyloid and cytokine profile in women with Alzheimer's disease. *Neuroendocrinol Lett*. **29**(1): 75-79.

10 Collins MM, Corcoran P, Perry IJ (2009). Anxiety and depression symptoms in patients with diabetes. *Diabet Med*. **26**(2): 153-161.

11 Dungan KM, Braithwaite SS, Preiser JC (2009). Stress hyperglycaemia. *Lancet*. **373**(9677): 1798-1807.

12 Izydorczyk B & Rybicka-Klimczyk A (2009). Cognitive aspects of women's body image and eating disorders. *Endokrynol Pol*. **60**(4)**:** 287-294.

13 Janocha A, Pilecki W, Bolanowski M, Małyszczak K, Salomon E, Laszki-Szcząchor K, et al (2009). Interhemispheric cerebral asymmetry detected by VEPS in diabetic patients with recognized depression. *Neuroendocrinol Lett*. **30**(1): 119-124.

14 Laron Z (2009). Insulin and the brain. *Arch Physiol Biochem*. **115**(2): 112-116.

15 Ruis C, Biessels GJ, Gorter KJ, van den Donk M, Kappelle LJ, Rutten G (2009). Cognition in the early stage of type 2 diabetes mellitus. *Diabetes Care*. **32**(7): 1261-1265.

16 Roriz-Filho J, Sá-Roriz TM, Rosset I, Camozzato AL, Santos AC, Chaves ML, et al (2009). (Pre)diabetes, brain aging, and cognition. *Biochem Biophys Acta*. **1792**(5): 432-443.

17 Stockhorst U, de Fries D, Steingrueber HJ, Scherbaum WA (2004). Insulin and the CNS: effects on food intake, memory, and endocrine parameters and the role of intranasal insulin administration in humans. *Physiol Behav*. **83**(1): 47-54.

18 Szabó M, Pelísková P, Kvapil M, Matous M (2009). Positive effect of long-term tailored physical activity therapy on diabetes mellitus management in an obese type 2 diabetic patient. *Neuroendocrinol Lett*. **30**(1): 22-24.

1 Takahashi T, Ikeda K, Ishikawa M, Kitamura N, Tsukasaki T, Nakama D, et al (2005). Anxiety, reactivity, and social stress-induced cortisol elevation in humans. *Neuroendocrinol Lett*. **26**(4): 351-354.Velemínský M Sr, Noll P, Hanzl M, Velemínský M Jr. (2008). Necrotizing enterocolitis in children with low birthweight induced with mucormycose strain. Neuroendocrinol Lett. **29**: 1021–1025.

2 Velemínský M Jr, Prádná J, Velemínský M Sr, Tosner J (2008a). Relationship of amniotic-type placenta inflammation to pPROM, PROM and risk of early onset neonatal sepsis. Neuroendocrinol Lett. **29**: 447–450.

3 Velemínský M Jr, Stránský P, Velemínský M Sr, Tosner J (2008b). Relationship of IL-6, IL-8, TNF and sICAM-1 levels to PROM, pPROM, and the risk of early-onset neonatal sepsis. Neuroendocrinol Lett. **29**: 303–311.

4 Velemínský M, Tosner J (2008). Relationship of vaginal microflora to PROM, pPROM and the risk of early-onset neonatal sepsis. Neuroendocrinol Lett. **29**: 205–221.

5 Verstraelen H, Goetgeluk S, Derom C, Vansteelandt S, Derom R, Goethebeur E, et al (2005). Preterm birth in twins after subfertility treatment: population based cohort study. BMJ. **19**: 331–337.