Correlation of Glycemic and Lipid Control Parameters with Cognitive Dysfunction Scores, in Type 2 Diabetic Persons

Results from a cross- sectional study

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Diabetes-related cognitive dysfunction is considered a long-term complication of diabetes. In this cross-sectional study was studied the relationship between cognitive dysfunction (assessed by using two standardized questionnaires), lipid profile parameters and fatty free acids intake, in outpatients, hospitalized for their periodical control. The Mini-Mental State Exam (MMSE) and The Montreal Cognitive Assessment (MoCA) score were related to the body mass index (BMI), high density cholesterol (HDLc), glycated hemoglobin (Hb A1c) and intake of choline and eicosapentaenoic acid (all Ps < .05, excepting the relationship between MMSE and HDL$_c$). The implications of FFA intake in dementia development, in type 2 diabetics, is important for disease management and prevention .

Keywords: The Mini-Mental State Exam (MMSE), The Montreal Cognitive Assessment (MoCA) body mass index (BMI), high density cholesterol (HDLc), glycated hemoglobin (Hb A1c), Type 2 Diabetes

Diabetes-related cognitive dysfunction may be viewed as another long-term complication of diabetes [1]. It is associated with mental and motor slowing and decrements of attention and executive functioning. Subcortical small-vessel disease (SSVD) is described from clinical, imaging and neuropathological viewpoints. SSVD is considered the most prevalent ischemic brain disorder. It's frequency increases with age [2].

Vascular risk factors include hypertension, diabetes, hyperlipidemia, elevated homocysteine, and obstructive sleep apnea. Ischemic white matter lesions are the hallmark of SSVD [3,4]. Cognitive impairement in type 2 diabetes is characterised by neural slowing, increased cortical atrophy, microstructural abnormalities in white matter tracts and changes in concentrations of brain neurometabolites [5,6]. Hypoglycemic crises and also long-term hyperglycemia leads to white matter (WM) impairment [7] and brain dysfunction [8].

In this observational study was studied the relationship between cognitive dysfunction (assessed by two standardized questionnaires) and lipide profile parameters in outpatients patients, hospitalised for their periodical control. The intake of lipids was evaluated by using 24 hours dietary recall (24HR) and related to serum lipids and cognitive scores. Finding a relationships would be useful to identify an algorithm for clinical practice, in disease prevention.

Experimental part

Materials and methods

We conducted a cross-sectional study in a sample of 138 type 2 diabetic patients, hospitalised for their annual control, during 2017. We created a pro forma for data collection that was completed during hospitalisation. We collected:

-Demographic data: age, gender, area of residence (urban or rural), family status (married or single,) and duration of formal education;

-The duration of diabetes, presence of chronic complications, type of treatment (insulin or oral agents);

-Anthropometric parameters: body mass index (BMI) and waist circumference;

-Laboratory findings: glycated hemoglobine (Hb A1c), cholesterol, high density cholesterol (HDLc), low density cholesterol (LDLc), triglycerides;

-Diet evaluation -24 h dietary recall (24-HR).

The Mini-Mental State Exam (MMSE) is a widely used test of cognitive function among the elderly; it includes tests of orientation, attention, memory, language and visual-spatial skills. Any subject with MMSE at or above 26 may be presumed competent unless listed otherwise at last evaluation.

The Montreal Cognitive Assessment (MoCA) is a widely used to detect cognitive impairment [9]. It was validated in the setting of mild cognitive impairment, and has subsequently been adopted in numerous other settings clinically. MoCA scores range between 0 and 30. A score of 26 or over is considered to be normal [10].

The data were included in a database using Microsoft Office Excel 2007. For statistical analysis we used SPSS programme (Statistical Package for Social Sciences) version 13.0 for Windows (Chicago, IL, USA). The Kolmogorov test was used to evaluate the normal distribution of the analyzed data. To assess the association between variables Spearman correlation coefficients were determined. ANOVA test (the distribution of the data was normal) was used to calculate if there were significant differences between the values of repeated measurements.

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Results and discussions

The participants were selected from type 2 diabetes outpatients of the Diabetes Centre in Iasi hospitalised for their annual control, in 2017. The main part of the patients were males (61.34%) and came from the urban environement (57.98%). An important proportion of them were overweight (27.3%) and obese (53.4%) and had a poor glycemic control (57.7%). The prevalence of mild cognitive impairment estimated by Mini-Mental State Exam (MMSE) was 19.7%. Using Montreal Cognitive Assessment (MoCA) the prevalence of the cognitive imairement was higher (37%).

The intake of essential fatty acids - eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) and choline were estimated by using 24 HR questionnaire. Dietary recommended intake (DRI) for choline is 400 mg/day and DRI for EPA and DHA is 500 mg/day according to European Food Safety Authority. A lower mean intake of these nutrients then recommended were noticed in this sample (table 1).

MMSE score and MoCA were related to the BMI, HDL cholesterol, Hb A1c and the intake of choline and EPA (all *P*s < .05, excepting the relation between MMSE and HDL) (table 2).

The diabetics with mild cognitive impairement had a lower daily intake of choline and eicosapentaenoic acid than patients which obtained a normal score at MMSE (p=0.001 and 0.046, respectively). A lower concentration of HDLc was noticed in patients with an abnormal MMSE score (p=0.026). The patients with cognitive disfunction had a higher BMI and waist circumference and a higher intake of docosahexaenoic acid (not significant reationships) (table 3).

	Minimum	Maximum	Mean	Std. Deviation
Age	20	66	54.92	8.92
Waist circumference	66	135	96.93	15.60
Cholesterol	86	333	184.21	46.94
HDL	10	89	41.31	18.74
Trigliceride	43	617	179.76	137.77
HbA1c	5	14	7.88	1.86
MMSE score	23	31	26.21	2.07
MoCA score	22	37	28.07	5.25
Choline mg	103	682	305.90	196.21
EPA g	0.00	0.67	0.17	0.19
DHA g	0.00	0.89	0.19	0.25
BMI	6.42	44.20	29.99	6.37

Table 1
DESCRIPTIVE CHARACTERISTICS OF THE PATIENTS

		MMSE score	MOCA score
Waist circumference	Correlation Coefficient	-.039	-.029
	Sig. (2-tailed)	.553	.654
BMI	Correlation Coefficient	**-.134***	**-.152***
	Sig. (2-tailed)	**.039**	**.019**
Cholesterol	Correlation Coefficient	.026	.040
	Sig. (2-tailed)	.711	.577
HDL	Correlation Coefficient	**.373****	.080
	Sig. (2-tailed)	**.000**	.412
Trigliceride	Correlation Coefficient	.111	.105
	Sig. (2-tailed)	.199	.224
HbA1c	Correlation Coefficient	**.177***	**.205***
	Sig. (2-tailed)	**.027**	**.010**
Coline (mg)	Correlation Coefficient	**.346****	**.519****
	Sig. (2-tailed)	**.000**	**.000**
EPA (g)	Correlation Coefficient	**.236***	**.269****
	Sig. (2-tailed)	**.018**	**.007**
DHA (g)	Correlation Coefficient	.185	.174
	Sig. (2-tailed)	.067	.086

Table 2
RELATIONSHIP BETWEEN COGNITIVE ASSESSMENT SCORES, LIPID PROFILE AND ESSENTIAL FATTY ACIDS INTAKE

		Mean	Std. Deviation	95% Confidence Interval for Mean		p
				Lower Bound	Upper Bound	
IMC	normal score	29.75	6.58	28.81	30.69	.24
	low score	30.97	5.44	29.37	32.57	
CA	normal score	96.55	15.85	94.29	98.82	.45
	low score	98.47	14.60	94.18	102.75	
Cholesterol	normal score	187.55	46.63	180.29	194.81	.38
	low score	170.03	46.17	154.85	185.21	
HDL	normal score	43.06	19.07	39.06	47.05	**.026**
	low score	32.06	14.01	24.86	39.26	
Trigliceride	normal score	186.51	145.15	159.08	213.94	.23
	low score	150.04	95.72	110.52	189.56	
HbA1c	normal score	7.98	1.95	7.63	8.33	.17
	low score	7.48	1.46	6.97	8.00	
Choline (mg)	normal score	326.91	194.69	299.12	354.70	**.001**
	low score	220.51	180.28	167.57	273.44	
EPA (g)	normal score	.17	.19	.13	.21	**.046**
	low score	.15	.21	.06	.26	
DHA (g)	normal score	.20	.24	.14	.25	.3
	low score	.17	.28	.04	.30	

Table 3
MILD COGNITIVE IMPAIRMENT (MMSE) ACCORDING TO CLINICAL AND BIOCHEMICAL EVALUATION

		Mean	Std. Deviation	95% Confidence Interval for Mean		p
				Lower Bound	Upper Bound	
BMI	normal score	29.08	6.70	28.00	30.17	**.004**
	low score	31.53	5.49	30.37	32.69	
WC	normal score	97.18	15.81	94.63	99.73	.75
	low score	96.51	15.30	93.27	99.75	
cholesterol	normal score	183.58	45.05	175.77	191.40	.79
	low score	185.38	50.63	173.21	197.54	
HDL	normal score	41.36	18.25	36.69	46.04	.97
	low score	41.24	19.59	35.42	47.06	
Trigliceride	normal score	191.22	149.82	160.70	221.74	.13
	low score	152.53	100.15	120.49	184.56	
HbA1c	normal score	8.30	1.96	7.89	8.71	**.001**
	low score	7.29	1.54	6.91	7.68	
Choline (mg)	normal score	373.48	188.93	343.00	403.96	**.001**
	low score	190.69	149.80	158.95	222.43	
EPA (g)	normal score	.20	.20	.15	.25	**.028**
	low score	.11	.17	. 06	.17	
DHA (g)	normal score	.24	.26	.17	.31	**.023**
	low score	.12	.21	.05	.19	

Table 4
MILD COGNITIVE IMPAIRMENT (MOCA) AND SAMPLE CHARACTERISTICS

Using MoCA evaluation, mild cognitive impairement was associated with BMI (p=.004), glicemic control (p=.001), choline intake (p=.001) and essential fatty acids (DHA – p=0.28; EPA- p=0,23). Lipid profile wasn't related with the cognitive impairement in this sample (table 4).

In this sample, the prevalence of mild cognitive impairment estimated by Mini-Mental State Exam (MMSE) was 19.7%. Using Montreal Cognitive Assessment (MoCA) the prevalence of the cognitive impairement was higher (37%). The Rotterdam study of over 6000 patients with type 2 diabetes showed a 2-fold increase in the risk for dementia [11].

In our study, cognitive dysfunction scores were related to the BMI, HDL cholesterol, Hb A1c, choline intake and EPA. The patients with cognitive dysfunction had a higher BMI and waist circumference. Hyperglycemia leads to increases in diacylglycerol and protein kinase C (PKC), which decreases the levels of endothelial nitric oxide synthase (eNOS) and thus lowers the bioavailability of nitric oxide (NO), leading to impaired vasorelaxation. PKC leads to the proliferation and migration of vascular smooth muscle cells (VSMCs), an important step in the development of atherosclerosis [12]. Studies have shown that patients with a HbA_{1C} of greater than 7% have a 4-fold increase in the development of mild cognitive impairment [13].

In many studies, the cognitive domains that were associated with impairment covered a wide range of abilities: processing speed, nonverbal memory, executive function (Edinburgh Type 2 Diabetes Study), psychomotor speed memory, verbal learning, executive function (Atherosclerosis Risk in Communities Study (ARIC), Action to Control Cardiovascular Risk in Diabetes-Memory in Diabetes (ACCORD-MIND) [12]. Cerebral microvascular disease may play a role in acceleration of cognitive decline in diabetes. The Edinburgh Type 2 Diabetes Study showed that microvascular disease is associated with cognitive decline in diabetes [14]. The severity of diabetic retinopathy was related to cognitive domains of verbal fluency, information processing speed and mental flexibility [14].

In our study, a lower concentration of HDL_c was noticed in patients with an abnormal MMSE score. Sun Y and all [15] showed that a higher serum concentration of high-density lipoprotein cholesterol (HDL_c) was associated with a better executive performance. Multilevel modeling showed that highest tertile of HDL_c was associated with better executive function.

HDL undergoes significant qualitative changes, both in structure and function, in diabetics [16] and has multiple important functions in brain. HDL dysfunction in central nervous system may directly induce cognitive impairment [17]. Some small particles of HDL e.g. apolipoprotein A-1 may cross the blood-brain barrier. The anti-oxidant and anti-inflammatory properties of apoA-I/HDL have been shown to play a significant role in neuroprotection. The association between HDL_{-C} levels and cognition could be attributed to the higher cardiovascular risk associated with lower HDL_{-C} [18].

The brain contains two main polyunsaturated fatty acids (PUFA): arachidonic acid (AA) and docosahexaenoic acid (DHA). Deficient diets in omega 3 PUFA lead to reduced DHA in the brain and increased turnover of AA to eicosanoids, an effect which is overcome by restoring the omega 3 PUFA to the diet. In neural trauma and neurodegenerative diseases, there is a dramatic rise in the levels of AA-derived eicosanoids. In contrast, DHA-derived compounds can prevent neuroinflammation [19]. In our study, the diabetics with mild cognitive impairement had a lower daily intake of choline and eicosapentaenoic acid. Using MoCA evaluation, mild cognitive impairement was associated with choline and essential fatty acids intake. This observational finding is biased by the design of the study. Clinical trials, with the registration of the FFA intake from multiple days should be realized to confirm this hypothesis [20-29].

Conclusions

In our study, abnormal scores of cognitive dysfunction were found in type 2 diabetics. They were correlated with glycemic control, high density cholesterol and free fatty acids intake. Underlying the implications of FFA intake in the development of dementia, in type 2 diabetics, is important in disease prevention. The results of our study should be confirmed by prospective studies or clinical trials.

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