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Original Research

Consequences of diabetes and pre-diabetes and the role of biochemical parameters of carbohydrate metabolism for the functioning of the prefrontal cortex in obese patients

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Abstract

Background: The role of executive functions (EF) is to maintain particular behaviours in order to achieve intended goals. EF are crucial in management of pre-diabetes, diabetes and obesity which are grievous diseases and can lead to severe complications. The aims of our study were to: assess EF in group of obese subject with carbohydrate disorders, evaluate whether biochemical factors and comorbidities related to metabolic disorders have adverse effect on EF in this group of patients. **Methods**: The study included 185 obese patients (146 women; 39 men) who were divided on three groups: pre-diabetic, diabetic and control subgroup. Patient underwent Wisconsin Card Sorting Test (WCST) to evaluate EF. Assessed biochemical factors included C-peptide, fasting plasma glucose (FPG) and glycosylated hemoglobin A1c (HbA1c). **Results**: Diabetic patients showed the worst WCST scores among the rest of groups. Pre-diabetic individuals did not differ in EF performance from control subgroup. We observed significant correlations between FPG and HbA1c and worse WCST scores in pre-diabetic subgroup. In diabetic patients C-peptide correlated with poorer EF. Depressive symptoms and hypertension significantly correlated with non-perseverative errors in WCST. **Conclusions**: The subgroup of diabetic patients were the most obese and had the worst glycemia parameters. They also showed the worst EF in WCST. According to obtained results, hyperglycemia positively correlated with poor EF in pre-diabetes. However, in diabetic subjects cognitive deterioration may results from insulin resistance rather than hyperglycemia. In obese individuals with carbohydrate disorders both hypertension and depressive symptoms significantly contributed to EF dysfunction.

Keywords: executive functions; WCST; T2DM; pre-diabetes; obesity; cognitive functions

1. Introduction

Modern advances in many fields, such as medicine have improved daily lifestyle. However, better life conditions, sedentary lifestyle, easiness in obtaining food with high amounts of calories contribute to the development of metabolic diseases—obesity and diabetes mellitus.

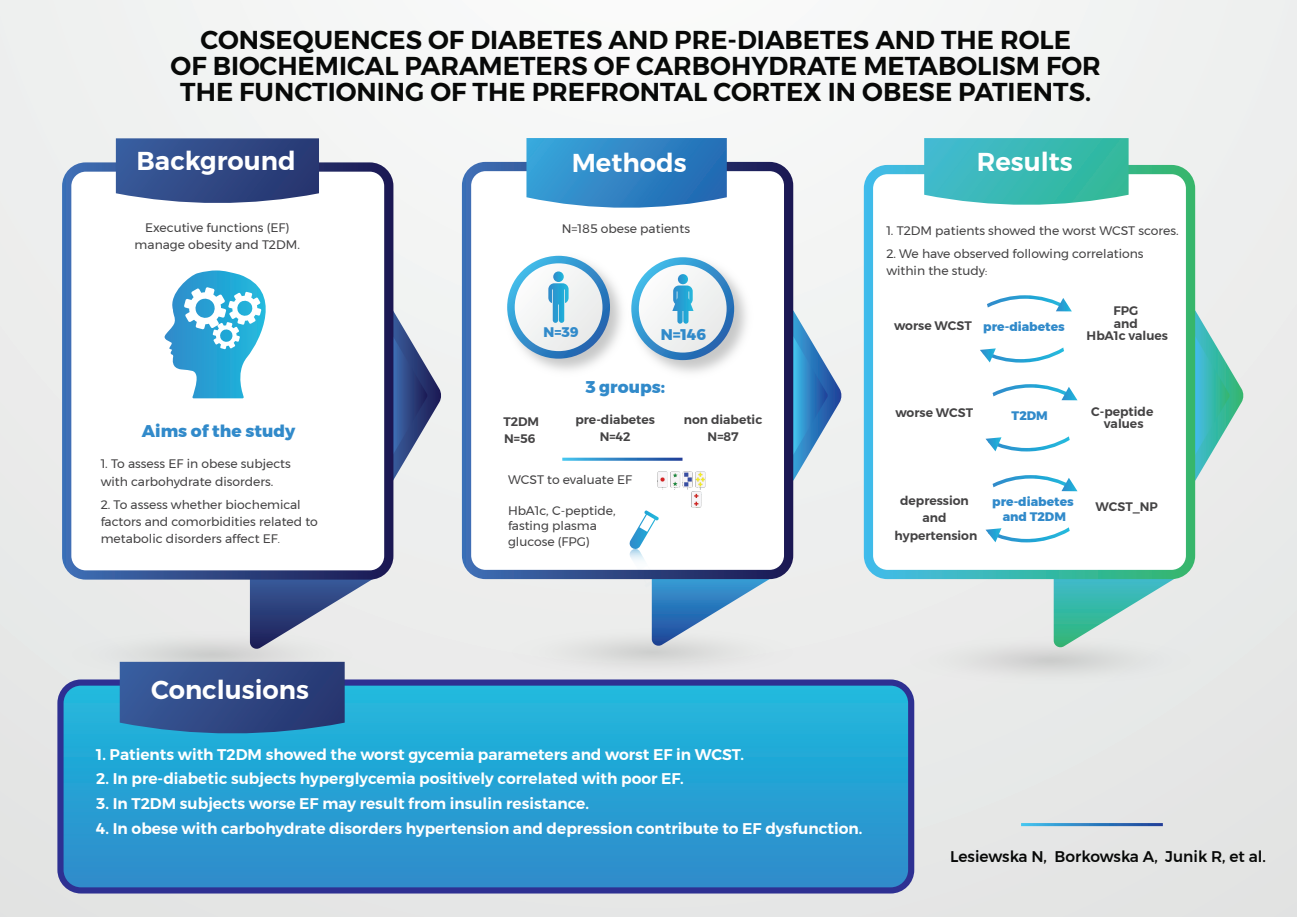
According to WHO, we are currently struggling with obesity crisis. Data show that in 2016 more than 1.9 bilion adults were overweight, (650 milion of them were obese); regarding children and adolscents, over 340 milions of them were overweight or obese [1].

International Diabetes Federation estimates that 1 in 11 adults (463 million people) suffers from diabetes mellitus, one fifth of diabetic patients are above 65 y.o., and nearly 374 milion people have impaired glucose tolerance (IGT) [2]. Those numbers are alarming and, if neglected, will be rising every year.

Both, obesity and diabetes mellitus are associated with grevious complications which can contribute to greater mortality and such as cardiovascular disease (CVD) [3–7]. Research also show the interplay between type 2 diabetes mellitus (T2DM), obesity and the pathogenesis of depression indicating that mental disorders are risk factor of metabolic diseases and vice versa [8].

An important element in the long-term therapy of patients with T2DM is glycemic control, which is an expression of compliance with treatment. The factors related to glycemic control include demographic factors such as sex, age, education, ethnicity, but also clinical parameters such as duration of T2DM and psychological parameters such as depressive symptoms or executive functions (EF) [9–12].

In neuropsychology, all abilities which allow people to take actions in order to achieve their goals, is the set of high cognitive processes called executive functions [13,14]. EF take part in actions associated with planning, making decisions, monitoring errors and correcting them, as well as performing complex actions by dividing particular steps in proper sequences. One uses them during inhibiting some



Visual Abstract. EF, executive functions; T2DM, type 2 diabetes mellitus; WCST, wisconsin card sorting test; FPG, fasting plasma glucose; WCST_NP, % of non perseverative errors of wisconsin card sorting test; HbA1c, hemoglobin A1c.

habitual responses or during resisting themselves from the rewarding stimuli [15]. EF may be divided on attentional control, inhibitory control, cognitive inhibition, cognitive flexibility and working memory [16,17]. Patients use EF to keep proper and healthy diet, stop themselves in eating high carbohydrate foods or plan their day to maintain the balance between physical activity and meals to control appropriate glucose levels in blood and therefore, EF are crucial in managing obesity and diabetes.

Evidence demonstrate that T2DM increases the risk of cognitive decline and dementia [18]. Yeung *et al.* [19] showed that in comparison to healthy individuals, T2DM patients gained significantly poorer results in tests assessing executive functions. A meta-analysis reported that T2DM was associated with significantly worse performance in following cognitive domains: EF, speed processing, psychomotor performance and verbal learning [20]. Diabetes affects cognition on many ways-factors which may inflict damage on brain functions are the duration of the diabetes or the levels of glycemia. Results of Maastricht Aging Study showed greater cognitive deterioration in diabetic subjects in comparison to healthy ones over the period of 12 years [21]. Another study demonstrates that elevated levels of glycosylated hemoglobin were significantly associated with poorer cognitive performance in the group of diabetic patients [22].

There are also reports describing the association between specific cognitive functions with poorer control of T2DM [23,24]. In the elderly population these were memory impairment and executive dysfunction which lead to the progression of the disease. An important element is the bidirectional dependence of diabetes mellitus and cognitive functioning, due to evidence that diabetes affects the function and structure of the brain [25–27].

Obesity also has been linked with poorer cognitive functioning. Data point to the linkage between excessive weight and deterioration in attention, memory and visuaspatial domains [28–30]. Gathered evidence show that obese individuals present worse EF in comparison to healthy controls. The scrutinized connections between obesity and EF suggest that the poorer cognitive performance in those domains may be the culprit of further weight gain [31,32].

Some evidence however, show mixed results regarding the influence of the obesity on cognition. In comparison to normal-weight, obese participants had better performance in tasks assessing visuospatial speed [33]. De-

schamps *et al*. [34] in their follow-up study found lower risk of cognitive decline in overweight subjects. Hence, more research is needed in this field.

As stated before, numbers of patients who are suffering from both obesity and T2DM are growing and assessment of cognitive functions might bring promising data which then could be utilized in order to create better treatment plans or preventive programmes. Hence, the aim of this study was to assess the EF in obese individuals with T2DM and pre-diabetes in comparison to "healthy" obese controls. We also evaluated whether biochemical factors related to glycemia and insulin affect EF. The last step of our analysis was to evaluate if diseases related to obesity and diabetes take part in EF deterioration in this group of patients.

2. Materials and methods

2.1 Participants

The study was conducted in a group of 185 Caucasian people (146 women; 39 men) who were under outpatient care in Endocrinology and Diabetology Clinic due to primary obesity. All patients were tested for carbohydrate disorders. Analyzing the history of the disease and the results of the oral glucose tolerance test (OGTT), the patients were divided into three groups: in the first group there were 87 patients without carbohydrate disorders (65 women and 22 men), in the second group—42 patients with impaired glucose tolerance (IGT) or impaired fasting glycemia (IFG) (33 women and 9 men) and in the third 56 patients (48 women and 8 men) with diabetes. The median age was the highest in the subgroup of people with diabetes, and this group was also the most severe. Demographic characteristics are shown in Table 1.

The following inclusion criteria were adopted in the study: adulthood (age between 16 and 69 y.o.), consent to study participation and primary obesity. Secondary causes of obesity were excluded due to performed medical assessment and the results of metabolic and hormonal tests. Serious psychiatric or neurological illnesses, addictions to any illicit drugs or alcohol, or any significant somatic diseases like cardiovascular disease, were implemented as exclusion criteria.

We provided participants with detailed information about the objectives and nature of the study before obtaining their written informed consent to participate. The Bioethics Committee at Nicolaus Copernicus University has agreed to conduct the study (No. 533/2008).

2.2 Clinical assessments and measures

Obesity was diagnosed on the basis of anthropometric measurements and the calculation of the body mass index (BMI). BMI is an indicator of body fat concentration and is calculated as weight (kg) squared height (m). Disorders related to impaired glucose metabolism were diagnosed with an oral glucose tolerance test performed with 75 g of anhydrous glucose in solution. If a patient had a history of diabetes and received appropriate treatment, the patient was included in the diabetes group. Glucose was obtained initially, before glucose load, and two hours after glucose ingestion. Patients fasted for at least 8 hours prior to the OGTT.

Based on the OGTT results, patients were assigned to individual study subgroups:

(1) if the fasting glucose level was below 99 mg% (5.5 mmol/L), and after two hours below 140 mg% (7.8 mmol/L), the patient was not diagnosed with carbohydrate disturbances.

(2) if the patient had elevated fasting blood glucose levels above 100 mg% and the result was normal after two hours, the patient had abnormal fasting glucose and was assigned to the IFG/IGT group.

(3) if the patient had a blood glucose level of 140–199 mg% (7.8–11.1 mmol/L) after 2 hours, he was diagnosed with impaired glucose tolerance and was included in the IFG/IGT group.

(4) if the blood glucose concentration was above 200 mg% (11.1 mmol/L) after 2 hours, the patient was diagnosed with diabetes mellitus

In order to determine the control of diabetes, the level of glycosylated hemoglobin A1c (HbA1c) was determined in the study population. It is considered a good indicator of glycemic control in the last two to three months [35]. Fasting plasma glucose (FPG) and C-peptide were also determined as complementary biochemical analyzes.

2.3 Psychological assessment

To assess the functioning of the prefrontal cortex, in particular working memory and executive functions, a computer version of the Wisconsin Card Sorting Test (WCST) with instructions in Polish was used. The WCST analysis was based on the following parameters: (1) the percentage of perseverance errors (WCST_P), reflecting thinking rigidity and difficulties in adapting to changing conditions; (2) the percentage of non-perseverance errors (WCST_NP), which is the number of errors reflecting the effectiveness of attention (reflecting disordered responses); (3) the number of completed categories (WCST_CC), which is related to the efficiency of thinking; expresses the ability to react correctly on the basis of the new information received, experience gained and feedback signals; (4) the number of cards needed to compose the first category (WCST_1st), as an expression of the proficiency in formulating a logical concept; (5) the percentage of responses consistent with the logical concept (WCST_CLR), it is a parameter reflecting the ability to maintain the applied logical concept and shows the ability to plan activities based on the information received. WCST and its parameters selected for analysis are considered reliable in the assessment of the prefrontal cortex function [36].

Table 1. Demographic and clinical parameters in study subgroups.

	Nondiabetic (n = 87)	IFG/IGT (n = 42)	Diabetic (n = 56)	*p*	Post hoc
Gender (♀/♂)	65/22	33/9	48/8	0.69	ns.
Age (y)	35.0 (18.0–68.0)	42.0 (18.0–69.0)	52.0 (31.0–61.0)	<0.0001	Nondiabetic vs. IFG/IGT $p = 0.00004$ Nondiabetic vs. Diabetic $p < 0.00001$ IFG/IGT vs. Diabetic $p = 0.0004$
BMI	41.5 (30.1–64.1)	42.5 (31.2–58.6)	48.9 (35.5–61.3)	0.0036	Nondiabetic vs. IFG/IGT $p = 0.83$ Nondiabetic vs. Diabetic $p = 0.002$ IFG/IGT vs. Diabetic $p = 0.003$
Degree of obesity (n, %)	I—0 (11.5%) II—3 (26.5%) III—4 (62%)	I—5 (12%) II—12 (28.5%) III—24 (59.5%)	I—8 (14%) II—18 (32%) III—30 (54%)	0.025	Nondiabetic vs. IFG/IGT $p = 0.73$ Nondiabetic vs. Diabetic $p = 0.01$ IFG/IGT vs. Diabetic $p = 0.01$
Hypertension (n, %)	21 (24%)	22 (52.4%)	28 (50%)	<0.0001	Nondiabetic vs. IFG/IGT $p = 0.001$ Nondiabetic vs. Diabetic $p < 0.00001$ IFG/IGT vs. Diabetic $p = 0.03$

Kruskal Wallis ANOVA; Post hoc analysis, Fischer NIR test.

Table 2. Metabolic results in study subgroups (median and range).

	Nondiabetic (n = 87)	IFG/IGT (n = 42)	Diabetic (n = 56)	*p*	Post hoc
Fasting glucose (mg/dL)	88.0 (71.0–99.0)	103.0 (81.0–124.0)	130 (98–215.0)	<0.0001	Nondiabetic vs. IFG/IGT $p < 0.00001$ Nondiabetic vs. Diabetic $p < 0.00001$ IFG/IGT vs. Diabetic $p < 0.00001$
C-peptide level (nmol/L)	2.44 (0.28–11.8)	3.36 (0.22–101.0)	4.08 (0.33–101.0)	0.026	Nondiabetic vs. IFG/IGT $p = 0.28$ Nondiabetic vs. Diabetic $p = 0.03$ IFG/IGT vs. Diabetic $p = 0.16$
HbA1c (%)	5.4 (4.36–6.5)	5.8 (5.0–7.2)	7.8 (4.84–8.7)	<0.0001	Nondiabetic vs. IFG/IGT $p = 0.001$ Nondiabetic vs. Diabetic $p < 0.00001$ IFG/IGT vs. Diabetic $p < 0.00001$

Kruskal Wallis ANOVA; Post hoc analysis, Fischer NIR test.

Table 3. WCST results in study subgroups (median and range).

	Nondiabetic (n = 87)	IFG/IGT (n = 42)	Diabetic (n = 56)	*p*	Post hoc
%Pers	10.0 (4.0–48.0)	10.5 (6.0–38.0)	14.0 (6.0–36.0)	0.03	Nondiabetic vs. IFG/IGT $p = 0.37$ Nondiabetic vs. Diabetic $p = 0.005$ IFG/IGT vs. Diabetic $p \leq 0.05$
%N_Pers	11.0 (3.0–59.0)	9.5 (1.0–33.0)	15.0 (7.0–36.0)	0.0478	Nondiabetic vs. IFG/IGT $p = 0.28$ Nondiabetic vs. Diabetic $p = 0.16$ IFG/IGT vs. Diabetic $p = 0.045$
%CLR	74.0 (0.0–91.0)	73.0 (6.0–89.0)	65.5 (9.0–84.0)	0.047	Nondiabetic vs. IFG/IGT $p = 0.84$ Nondiabetic vs. Diabetic $p = 0.03$ IFG/IGT vs. Diabetic $p = 0.08$
CC	6.0 (0.0–6.0)	6.0 (0.0–6.0)	5.0 (0.0–5.0)	0.08	ns.
1st Cat	12.0 (10.0–129.0)	12.0 (10.0–129.0)	12.0 (11.0–129.0)	0.74	ns.

%Pers, the percentage of perseverative errors; %N_Pers, the percentage of non-perseverative errors; %CLR, the percentage of responses consistent with the logical concept; CC, the number of completed categories; 1st Cat, the number of cards needed to compose the first category; IFG, impaired fasting glucemia; IGT, impaired glucose tolerance.

2.4 Statistical analysis

The data were tested using the Shapiro-Wilk test and it was found that the study group did not meet the criteria of a normal distribution. The statistical significance of differences between the 3 groups was tested by Kruskal-Wallis analysis of variance (ANOVA). Post hoc analysis was performed using the Fisher NIR test. Correlation analysis was performed using the R-Spearman correlation test. In order to perform the multivariate analysis, a multiple regression model was used. Statistica 13.0 (StatSoft Polska, Krakow, Poland) was used for statistical analyzes.

3. Results

The parameters related to the occurrence of disorders of carbohydrate metabolism and their advancement were obviously higher in the IFG/IGT group and the highest in the diabetes subgroup (Table 2).

The analysis of the results obtained in the WCST subgroups revealed significantly more perseverative and non-perseverative errors and significantly fewer death responses with the logical concept in the diabetes subgroup (Table 3). There were no significant correlations between WCST results and biochemical parameters in the obese subgroup without carbohydrate disorders.

There were no significant correlations between WCST results and biochemical parameters in the obese subgroup without carbohydrate disturbances. In the IFG/IGT and diabetes subgroups, there were numerous significant correlations between worse WCST scores and poorer fasting glucose, HbA1C and C-peptide parameters (Table 4).

In order to confirm the significance of the participation of carbohydrate disturbances in the WCST results, the analysis of the multiple regression model was performed. This analysis confirmed that age is the most common factor influencing the outcome. In addition, it was found that HbA1c was significant in the context of WCST_% Pers, hypertension and depressive symptoms in WCST_% N_Pers, and depressive symptoms in terms of WCST_1st Cat (Table 5).

4. Discussion

The aim of this study was to scrutinize the EF in obese individuals with pre-diabetes and T2DM. In our assessment we also took into consideration biochemical factors i.e., glycemia and insulin resistence (C-peptide, FPG, HbA1c), and other comorbidities related to metabolic disorders like hypertension and depression. In the next step of our analysis, we performed calculations in order to find associations between abovementioned factors and the performance of executive functions measured with WCST.

Literature has reported relationship between obesity and cognitive deterioration. The study of Gunstad *et al.* [37] showed that healthy individuals who were overweight or obese had worse scores in tools assessing EF. However, researchers did not observe any associations between attention domains [37]. Also being obese is associated with cognitive deficits in other domains like psychomotor, attention, memory, verbal fluency, or visuomotor skills [38–42]. Neuroimaging studies confirm those examples by observing changes in brain structure in obese people. Decreased regional cerebral blood flow in prefrontal cortex in obese individuals may be responsible for deteriorations of EF and attention [43]. Data show relationship between greater BMI and lower grey matter volume, as well as changes in white matter which supports hypothesis of putative acceleration of brain aging in obese people, which lead to cognitive decline [44,45]. This is consistent with results of our study presented in Table 3. The group of T2DM were the most obese and showed the worst performance in WCST.

Table 4. R-Spearman correlations WCST scores in women and men. Partial Kendall regression for significant correlations.

RESULTS IN NONDIABETIC PATIENTS						
	Fasting glucose [mg/dL]	*p*	C-peptide level [nmol/L]	*p*	HbA1c (%)	*p*
%Pers	0.009	0.93	0.063	0.56	0.147	0.17
%N_Pers	0.217	0.04	0.020	0.85	–0.035	0.74
%CLR	–0.208	0.05	0.053	0.62	0.020	0.85
CC	0.020	0.85	0.214	0.04	0.054	0.61
1st Cat	0.153	0.15	0.054	0.61	0.0001	0.99
RESULTS IN IGT/IFG PATIENTS						
	Fasting glucose [mg/dL]	*p*	C-peptide level [nmol/L]	*p*	HbA1c (%)	*p*
%Pers	0.327	0.03	0.301	0.05	0.445	0.003
%N_Pers	0.212	0.17	0.294	0.06	0.314	0.04
%CLR	–0.526	<0.001	–0.135	0.43	–0.446	0.003
CC	–0.458	0.002	–0.385	0.01	–0.448	0.003
1st Cat	0.100	0.52	0.071	0.65	0.180	0.25
RESULTS IN DIABETIC PATIENTS						
	Fasting glucose [mg/dL]	*p*	C-peptide level [nmol/L]	*p*	HbA1c (%)	*p*
%Pers	0.102	0.45	0.386	0.003	0.227	0.09
%N_Pers	–0.120	0.37	0.572	<0.0001	0.198	0.14
%CLR	–0.247	0.06	–0.449	0.0005	–0.247	0.06
CC	–0.327	0.01	–0.495	0.0001	–0.326	0.01
1st Cat	0.344	0.009	0.239	0.07	0.344	0.009

%Pers, the percentage of perseverative erroros; %N_Pers, the percentage of non-perseverative errors; %CLR, the percentage of responses consistent with the logical concept; CC, the number of completed categories; 1st Cat, the number of cards needed to compose the first category; IFG, impaired fasting glucemia; IGT, impaired glucose tolerance.

However, obesity is not a single factor affecting cognitive performance in this group. Literature presents findings linking T2DM with cognitive deterioration. The study of Redondo et al showed that in comparison to healthy individuals, persons with T2DM gained worse scores in tests evaluating EF (including WCST). These findings point to deleterious effects of T2DM on cognitive performance, even though T2DM subjects did not have elevated HbA1c values [46]. Moreover, authors of the publication emphasize that the exacerbation of EF presented in diabetic patients was similar to cognitive decline of patients with Alzheimer's disease. Results indicate the close relationship between T2DM and the pathogenesis of Alzheimer's. Not to mention, that Alzheimer's disease is named "Type 3 Diabetes" due to disturbances in insulin and glucose metabolisms in central nervous system [47,48].

Our results are also consistent with other findings in the literature, showing that comparing to healthy individuals, diabetic subjects were characterized with cognitive deficits in domains of executive functions [19,49,50].

Neuroimaging studies present evidence pointing to deleterious impact of diabetes on cognition, as indicated worse performance in utilized neuropsychological tests. Brains of pre-diabetic and diabetic individuals showed decreased activation in prefrontal cortex (PFC) during cognitive tasks in comparison to healthy subjects [51]. Diffusion Tensor Imaging method showed neuronal microstructural abnormalities in patients with T2DM in brain regions (including frontal lobes) which are responsible for domains like memory, attention, speed processing and EF [52]. Especially changes in PFC may be linked to poorer results in tests evaluating working memory, as shown in the study of Huang *et al*. [53].

Table 4 presents correlations between WCST parameters and biochemical factors of diabetes. We gained interesting findings in the subgroup of pre-diabetic patients. Worse EF performance in WCST domains positively correlated with greater plasma glucose levels and worse glycemia control measured with HbA1c levels. Regarding pre-diabetes and cognitive functions, studies show mixed results [54,55]. However, reports point to the association between pre-diabetes and minor cognitive deterioration in aspect of processing speed and EF. The study of Dybjer *et al.* [56] observed associations between cognitive deterioration in diabetic and pre-diabetic group, also in context of glucose levels measured during oral glucose tolerance test. Findings indicate that IFG was linked to worse cognitive tests results implying that inadequate glucose metabolism resulting in hyperglycemia may be responsible for cognitive deterioration. Furthermore, FPG and glycemia measured after 2 hours were also associated with cognitive performance. This is in line with our findings, showing that higher values of FPG levels and HbA1c in pre-diabetic group correlated with worse WCST performance. However, authors

Table 5. Multiple regression model for WCST results.

WCST_%Pers	B coefficiency	*p*	95% C.I. Lower	95% C.I. Upper
Gender	–0.043	0.71	–0.28	0.19
Age	0.241	0.11	–0.05	0.54
BMI	–0.041	0.84	–0.47	0.39
Hypertension	–0.078	0.58	–0.36	0.20
Fasting glucose	–0.190	0.26	–0.52	0.14
HbA1C	0.428	0.009	0.10	0.74
C-peptide	0.067	0.58	–0.17	0.31
BDI	0.198	0.35	–0.23	0.62
WCST_%N_Pers	B coefficiency	*p*	95% C.I. Lower	95% C.I. Upper
Gender	–0.090	0.40	–0.30	0.12
Age	0.428	0.002	0.15	0.70
BMI	–0.135	0.50	–0.53	0.26
Hypertension	0.308	0.02	0.04	0.57
Fasting glucose	–0.192	0.21	–0.49	0.11
HbA1C	0.034	0.81	–0.25	0.32
C-peptide	–0.073	0.51	–0.29	0.15
BDI	0.363	0.02	–0.02	0.75
WCST_%CLR	B coefficiency	*p*	95% C.I. Lower	95% C.I. Upper
Gender	0.093	0.41	–0.13	0.32
Age	–0.336	0.02	–0.62	–0.04
BMI	0.060	0.77	–0.36	0.48
Hypertension	–0.180	0.20	–0.45	0.09
Fasting glucose	0.178	0.27	–0.14	0.50
HbA1C	–0.248	0.11	–0.55	0.06
C-peptide	0.050	0.67	–0.18	0.29
BDI	–0.270	0.20	–0.68	0.14
WCST_CC	B coefficiency	*p*	95% C.I. Lower	95% C.I. Upper
Gender	–0.118	0.29	–0.34	0.10
Age	–0.394	0.007	–0.68	–0.10
BMI	0.085	0.68	–0.33	0.50
Hypertension	–0.115	0.40	–0.38	0.16
Fasting glucose	0.201	0.21	–0.12	0.52
HbA1C	–0.221	0.15	–0.52	0.08
C-peptide	0.076	0.51	–0.15	0.31
BDI	–0.369	0.04	–0.78	0.04
WCST_1st Cat	B coefficiency	*p*	95% C.I. Lower	95% C.I. Upper
Gender	0.143	0.22	–0.09	0.38
Age	0.385	0.01	0.08	0.68
BMI	–0.222	0.31	–0.66	0.21
Hypertension	–0.222	0.15	–0.07	0.49
Fasting glucose	–0.236	0.16	–0.57	0.10
HbA1C	–0.091	0.56	–0.41	0.22
C-peptide	–0.128	0.30	–0.37	0.11
BDI	0.146	0.49	–0.28	0.57

%Pers, the percentage of perseverative errors; %N_Pers, the percentage of non-perseverative errors; %CLR, the percentage of responses consistent with the logical concept; CC, the number of completed categories; 1st Cat, the number of cards needed to compose the first category; BMI, body mass index; BDI, Beck Depressive Inventory.

of the previous study also admit, that having diabetes for the prolonged time should be responsible for profound cognitive deficits [56].

Pre-diabetes is characterized with inappropriate glucose regulation leading to glucose imbalance reflected in hyperglycemia, as well as improper insulin metabolism which may promote insulin resistance. Nonetheless, such dysregulation, albeit greater than normal, can't be classified as diabetic. Results presented in Table 4 show, that within the group of pre-diabetic patients, the FGP and HbA1c were

significantly linked to worse WCST performance. Even though, the pre-diabetic patients did not differ in WCST scores in comparison to healthy individuals (Table 3), the metabolic changes in patients in pre-diabetic stage seems to contribute to worse cognitive performance in EF measured with WCST [57]. Those findings are in concordance with the literature. Studies show that even in persons without diabetes, higher glucose values were related to greater risk of dementia [58]. Also, greater values of glucose blood levels (even within normal ranges) were associated with lower grey and white matter volumes in magnetic resonance imaging (MRI) studies of healthy individuals—however the study group included individuals in their 60s [59]. Another studies point to FPG as an important factor of cognitive decline in individuals with metabolic syndrome, as well as in pre-diabetic patients with IFG [60,61]. Another important aspect is the connection between overweight, obesity or metabolic syndrome and worse EF performance [62]. Also in the stage of pre-diabetes, vascular dysfunctions may develop and affect brain function. Results of Maastricht Study revealed that pre-diabetes was linked to microvascular changes. Moreover, HbA1c and glucose levels were associated with vascular dysfunction which may contribute to neuropathy and further cognitive decline [63]. To sum up, our results suggest that cognitive decrements induced by obesity may be exacerbated by additional changes caused by greater glycemia values in pre-diabetes.

As shown in Table 4, also HbA1c values significantly correlated with some of the WCST scores associated with worse EF performance. Literature show mixed results in this regard. Study of Cukierman-Yaffe *et al.* [22] points to the inverse associations between HbA1c values and cognitive performance evaluated with battery of neuropsychological tests. Also greater HbA1c correlatated with greater risk to dementia, especially when the levels of HbA1c exceed 7% [64,65]. Nonetheless, results of other studies present opposite findings. In their study, Ruis *et al.* [66] did not find any relations between HbA1c values and cognitive performance. In the work of Nazaribadie *et al.* [57] were observed only significant correlations between HbA1c values and greater scores of perseverative errors in group with T2DM. In the study comparing the EF performance between patients with Alzheimer's disease and T2DM, group of T2DM showed decline in WCST even though they presented good glycemic control. Such outcome suggests that different mechanisms may be responsible for cognitive decline similar to AD patients and that T2DM patients with good glycemic control may still be at risk in developing AD [46]. Proposed mechanisms resposible for cognitive deterioration in diabetic patients are presented in the work of Cukierman-Yaffe *et al.* [67]. Among them, authors include the role of insulin in cognitive performance. Our results (Table 4) indicate significant correlations between greater insulin resistance (reflect by C-peptide values) and worse WCST scores, i.e., deterioration in EF. Those findings are in concordance with results in the literature which describe the dependence between insulin metabolism and cognition.

Hyperinsulinemia and insulin resistance are detrimental for brain function for many reasons. One of them is that insulin contribute to the excess of Advanced Glycation End products (AGEs) which impair the wall of blood vessels and in this manner may hinder proper blood flow in brain or downregulate neurogenesis, which in turn may be resposible for exacerbated memory [68]. Also accumulation of AGEs has been proposed as the main factor of glucotoxicity which may cause cognitive deficits similar to AD [69]. Other studies show, that insulin resistance may be responsibile for Alzheimer-like cognitive deficits in diabetic patients. Proposed mechanism is that insulin resistence via activation of metabolic processes, leads to the creation of neurofibrillary tangles and hence contribute to cognitive deterioration [70].

However, the Maastricht study did not confirm associations with HOMA test or C-peptide and fasting plasma insulin concentrations with cognitive performance among patients with T2DM and good glycemic control. Authors proposed that peripheral insulin resistance may be unrelated to cognitive functions in the group of T2DM subjects, and cerebral insulin resistance may be responsible for cognitive deterioration in diabetic individuals [71].

Obesity is associated with hyperinsulinemia as well, and may lead to neurocognitive dysfunction by mechanisms described above. Building on results of our study it seems, that insulin resistance is strongly associated with deterioration of EF in obese individuals with T2DM rather than hyperglycemia [72,73]. However, more studies are needed to confirm these findings.

It is important to mention the other factors which have crucial impact on cognitive deterioration in patients with diabetes and which were not included within study analysis. Among them we can mention hypoglycemia, type of exercise or sleep deprivation [74]. Stress may affect circadian rythm and elicit changes within endocrinne system and in this manner may lead to cognitive deterioration [75].

Table 5 shows results of the multiple regression model for WCST scores. Obtained results indicate that comorbidities related to T2DM and obesity are significantly correlated with EF measured with WCST. Furthermore, it seems that EF dysfunctions in this group of patients may result from different factors related to obesity and diabetes.

Many studies have showed associations beteween depressive disorders and worse executive functions [76–78]. In comparison to healthy individuals, depressed patients showed worse scores in WCST which is consistent with results of our study. Those premises are confirmed in MRI studies, whereas patients with depression were characterized with smaller grey and white matter in comparison to control group [79–81]. Those findings are of the great importance due to mutual interactions between depression and diabetes. Both depression and diabetes show similar patho-

physiological paths, like changes within hypothalamic-pituitary-adrenal axis leading to high cortisol level and finally insulin resistance [82,83]. Inflammatory system may be also involed in the bidirectional way in the pathogenesis of both diseases [84].

To emphasize the interdependent role of obesity, diabetes and depression, Mansur *et al*. [8] proposed the term "metabolic mood syndrome". Synergistic effect of all diseases may negatively affect PFC and in such manner ensue further deterioration in executive functions. Disturbances in EF may interfere with proper management of T2DM and lead to hindrance in adequate glycemia monitoring. Negative thoughts related to depression may affect working memory and disturb focusing on the goal—such as maintaining proper glucose levels [85,86]. Outcomes of our study also indicate that depressive symptoms are associated with worse EF and may contribute to the "metabolic mood syndrome".

Another disease comorbid with obesity and T2DM is hypertension and this disease may also be responsible for the impairment of EF. Our results indicate significant correlation between hypertension and greater percentage of non-perseverative errors in WCST. Reaserches evaluating EF established the detrimental role of hypertension in comparison to healthy individuals [87,88]. This is in line with our outcomes. The possible mechanism linking diabetes, hypertension and worse cognitive performance may be cerebrovascular dysfunction. Changes in endothelium which occur due to hyperglycemia and hyperinsulinemia, in participation with hypertension may lead to damage of brain vessels and vascular dementia [89–91]. Such results are particularly important, because hypertension and metabolic syndrome are modifiable factors and can be treated. Therefore, the general assessment of obese, diabetic patients aimed at the evaluation of hypertension risk might prevent those patients from cognitive decline related to vascular damage.

5. Conclusions

Apart from somatic disorders, pre-diabetes, T2DM and obesity have crucial influence on brain function. Results of our study indicate the important role of the biochemical factors in context of EF in different stages of glycemic dysfunction (i.e., pre-diabetes and diabetes). Moreover, it seems that different factors, such as disorders related to T2DM and obesity are engaged in poorer performance in WCST and hence EF decline. Such results are very interesting and promising, because both diabetes and obesity require proper management and prophylaxis, especially that the number of people suffering from them are growing with every day. Implementing lifestyle changes is challenging and requires patients' effort and proper support. Also patients need to maintain self-control and self-regulation—the goal directed behavior associated with proper motivation to achieve the chosen goal [92]. Therefore, the performance of EF on the highest level is particularly important and if disrupted, may lead to nocuous complications of both diseases, even death.

Furthermore, pre-diabetes, diabetes and obesity can be prevented and knowledge obtained from studies assessing cognitive functions might help in creating programmes aiming at prophylaxis of neurodegenerations or helping with patients' self-management and compliance. However due to mixed results and limitations associated with our study, more research is needed.

6. Limitations

Unfortunately, our research is burdened with several limitations. The study sample is relatively small and there is a considerable age difference between participants. Our research also lacks healthy non-obese and age-matched control group. Moreover, the study design contains following pitfalls: no information regarding smoking, education status and the duration of diabetes mellitus.

Abbreviations

IGT, Impaired Glucose Tolerance; IFG, impared fasting glycemia; T2DM, type 2 diabetes mellitus; CVD, cardiovascular disease; EF, executive functions; OGTT, oral glucose tolerance test; BMI, body mass index; HbA1c, glycosylated hemoglobin A1c; FPG, fasting plasma glucose; WCST, Wisconsin Card Sorting Test; WCST_P, the percentage of perseverative errors; WCST_NP, the percentage of non-perseverance errors; WCST_CC, the number of completed categories; WCST_1st, the number of cards needed to compose the first category; WCST_CLR, the percentage of responses consistent with the logical concept; PFC, prefrontal cortex; MRI, magnetic resonance imaging.

Author contributions

AB and RJ conceived the idea for the study. MB contributed to the design of the research. MB, KJ, NL and AK were involved in data collection. MB, NL, and AB analyzed the data. MB and NL wrote the manuscript. AB coordinated funding for the project. All authors contributed toward data analysis, drafting and critically revising the paper and agree to be accountable for all aspects of the work.

Ethics approval and consent to participate

We provided participants with detailed information about the objectives and nature of the study before obtaining their written informed consent to participate. The Bioethics Committee at Nicolaus Copernicus University has agreed to conduct the study (No 533/2008).

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Conflict of interest

The authors declare no conflict of interest.

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