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RESEARCH ARTICLE

Dopaminergic Genes Polymorphisms and Prefrontal Cortex Efficiency Among Obese People - Whether Gender is a Differentiating Factor?

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Abstract: ***Background*:** Obesity is a chronic condition associated with poorer cognitive functioning. Wisconsin Card Sorting Test (WCST) is a useful tool for evaluating executive functions. In this study, we assessed the association between dopaminergic gene polymorphisms: *DAT1 (SLC6A3)*, *COMT*Val158Met, *DRD4 (*48-bp variable number of tandem repeats - VNTR) and WCST parameters to investigate the functions of the frontal lobes in obese individuals.

***Objective*:** To find the significant correlations between polymorphisms of *DAT1*, *COMT*Val158Met, *DRD4* and executive functions in obese subjects.

***Method*:** The analysis of the frequency of individual alleles was performed in 248 obese patients (179 women, 69 men). Evaluation of the prefrontal cortex function (operating memory and executive functions) was measured with the Wisconsin Card Sorting Test (WCST). Separate analyzes were performed in age subgroups to determine different activities and regulation of genes in younger and older participants.

***Results*:** Scores of WCST parameters were different in the subgroups of women and men and in the age subgroups. Regarding the COMT gene, patients with A/A and G/A polymorphisms showed significantly better WCST results in WCST_P, WCST_CC and WCST_1st. Regarding *DAT1* men with L/L and L/S made less non-perseverative errors, which was statistically significant. In *DRD4,* significantly better WCST_1st results were found only in older women with S allele.

***Conclusion*:** Obtained results indicate the involvement of dopaminergic transmission in the regulation of prefrontal cortex function. Data analysis indicates that prefrontal cortex function may ensue, from different elements such as genetic factors, metabolic aspects of obesity, and hormonal activity (estrogen).

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1. INTRODUCTION

Obesity is considered as a chronic medical condition which is also seen as an urgent public health problem of current times. Unfortunately, little progress has been made in order to obtain better treatment results for patients struggling with losing weight. Many physicians are still uncertain whether obesity should be perceived as a disease or is rather a result of inappropriate behavior due to the occurrence of many comorbidities [1]. Primarily, obesity is associated with numerous severe complications, which include somatic conditions, such as cardiovascular diseases, diabetes or cancer [2]. Secondary, obese individuals show psychosocial consequences like a greater risk of falling for depression or anxiety [3,4]. Apart from mood disorders related to this disease, another psychosocial aspect includes cognitive functions.

In the human brain, the prefrontal cortex (PFC) is a key structure which controls executive functions (EF) [5]. Another function of PFC is to monitor the processes of other cortical and subcortical structures [6]. EF

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consists of higher cognitive processes which are necessary to maintain control over one's behavior in order to achieve chosen goals or make daily decisions [7,8]. To the group of those processes pertain attentional control, inhibitory control, cognitive inhibition, cognitive flexibility and working memory.

Excessive weight may have a negative impact on cognitive processes. It has been shown that patients with greater body mass index (BMI) demonstrated poorer cognitive functioning in the context of memory, attention or visuospatial domains [9,10,11]. The study of Coppin *et al*. (2014) showed that obese and overweight individuals showed poorer performance in task evaluating working memory in comparison to healthy subjects [12]. Even though obesity is associated with impaired cognitive functions, also poor EF may contribute to weight gain. Stinson *et al*. (2018) indicated that impairments in processes responsible for maintaining self-control may give rise to overconsumption of high-calorie food, resulting in future weight gain [13].

Dopamine (DA) is a key neurotransmitter in food intake control. Theories explaining the pathogenesis of obesity involve disturbances in DA signaling within the reward circuit which is responsible for motivation and reward-seeking behaviors. The results of our studies, showed correlations between dopaminergic genes polymorphisms (*DAT1*, *DRD4*) and BMI values, indicating that alleles involved in lower DA signaling were associated with greater weight, which supports the reward deficit theory of obesity [14,15,16,17].

The exact mechanism explaining poorer cognitive functioning in obese individuals remains unclear. Some theories suggest obesity-induced chronic inflammation processes or the involvement of microbiota composition [18,19,20]. Another concept is a dual process model which indicates that disturbances in EF (especially in inhibitory control) may exert hyperphagia, which may lead to obesity [21].

DA seems to contribute to more aspects of human behavior instead of only having the sole role in motivation [22]. It is also associated with diseases which show cognitive dysfunctions, including schizophrenia, Parkinson's disease, the attention deficit hyperactivity disorder (ADHD) or Alzheimer's disease [23-25]. Moreover, dopaminergic signaling influences the activity of PFC and frontostriatal networks [26,27]. In our study, we concentrated on polymorphisms in genes coding dopamine transporter, dopamine receptor D4 and catechol-O-methyltransferase (COMT) enzyme. Studies show the association between abovementioned gene polymorphisms with changes in cognitive processing. Lower striatal DAT availability determined by *DAT1* 9R (nine tandem repeats) influenced EF in patients with Parkinson's disease [28]. The Trail Making Test (TMT) Part A and B are neuropsychological tests allowing the assessment of various cognitive abilities, such as graphomotor skill and visual scanning, as well as executive function elements like working memory, set-shifting abilities or inhibition control [29]. Studies show, that obese individuals with 7R (seven tandem repeats) of *DRD4* performed worse in TMT B and TMT B-A scores, however, the sample of the study was relatively small [30].

Wisconsin Card Sorting Test (WCST) is a common neuropsychological test utilized for frontal lobe dysfunction in patients with brain lesions [31]. It measures executive functions, especially set-shifting between tasks, however, to complete the test, various abilities are required, such as attention, working memory or decision making [32]. Many studies question the sensitivity and specificity of the WCST to frontal lobe dysfunction in neurological and psychiatric patients [33,34]. Most neuroimaging studies show increased neural activity within the frontal or prefrontal area while performing the test. Nonetheless, the activation within parietal lobes has also been reported. Therefore, the execution of WCST involves abilities which pertain to different brain regions [35].

Given that *DAT1*, *COMT*Val158Met and *DRD4* are associated with susceptibility to obesity, and other diseases showing cognitive impairments. The aim of our study was to assess the correlation between cognitive functioning and these polymorphisms in the obese population. To our knowledge, this is the first study analyzing *DAT1* and *COMT*Val158Met polymorphisms and gender differences in the context of cognitive performance in the obese population.

2. PARTICIPANTS AND METHODS

2.1. Participants

The study group consisted of 248 Caucasian people, 179 women and 69 middle-aged men (standard deviation of 14 years for both men and women) with a diagnosis of primary obesity (mean BMI 42 kg/m^2 SD 7,9). Patients were recruited from the Obesity Treatment Clinic. Secondary causes of obesity were excluded on the basis of medical history, medical examination, clinical and laboratory tests (e.g., cortisol, prolactin, and thyroid-stimulating hormone levels). In addition, the existence of serious somatic and neurological diseases, psychiatric disorders and addictions are the exclusion criteria from the study. Demographic characteristics including age and sex of the subjects were collected (Table **1**). Participants were informed about the aims of this study and provided written consent of participation. The study was approved by the bioethical commission at the Nicolaus Copernicus University, Collegium Medicum in Bydgoszcz (No 533/2008).

2.2. Clinical Assessments and Measures

Significant clinical features were determined on the basis of physical examination and medical history. Particularly, carefully examined factors that may affect weight gain. In addition, data related to mental disorders and resulting from the biometric analysis were collected. Biometric analyzes were performed to measure body weight (kg), height (m) and BMI. As an

exponent reflecting the amount of body fat, the BMI was adopted. It was calculated as the ratio of mass (kg) to square height (m2). Obesity was defined as a BMI of or over 30 [36].

2.3. Neuropsychological Assessment

The assessment of the prefrontal cortex, especially working memory and executive functions was performed using a computerized version of the Wisconsin Card Sorting Test (WCST) with instructions in Polish. The following parameters were selected for analysis: (1) perseverative error percentage (WCST_P), it reflects the stiffness of thinking or the difficulty in adapting to changing conditions; (2) percentage of non-perseverative errors (WCST_NP), that is the number of errors related to the effectiveness of the attention function (it shows random reactions, unordered),; (3) the number of correctly completed categories (WCST_CC), this number reflects the effectiveness of thinking and expresses the ability to respond correctly based on received new information, gained experience and feedback signals; (4) the number of trials required to complete the first category (WCST_1st), which is an expression of proficiency in the formulation of a logical concept; (5) percentage of correct answers occurring in series of three or more (WCST_CLR), it is a parameter reflecting the ability to maintain the logical concept used, but also is the result of the ability to plan actions based on the information received. WCST and its parameters selected for analysis are considered reliable in the assessment of the prefrontal cortex function [37].

In order to analyze the effect of the polymorphisms on the WCST results in different age groups, the study groups were divided among women and men above and below the median age in the study group, i.e. 45 years.

2.4. Genotyping

Blood was collected and mixed with 0.5 mL of 0.5 M EDTA, frozen in liquid nitrogen, and stored at -80°C prior to extraction. Genomic DNA was extracted from 7 to 10 mL of peripheral blood using the method of Lahiri and Schnabel (1993) [36]. *DAT1, COMT* and *DRD4* genotypes were determined by polymerase chain reaction (PCR). The following primers were used: *DAT1* forward, 5′TGTGGTGTAGGGAACGGCCTGAG-3′; *DAT1* reverse, 5′-CTTCCTGGAGGTCACGGC TCAAGG-3′; *COMT* forward, 5′-AGCTCCAAGC GCGCTCACAG-3′; COMT reverse, 5′-CAAAGTGCG CATGCCCTCCC-3′; DRD4 forward: 5’-GCGACTACGT GGTCTACTCG-3’; and *DRD4* reverse: 5’-AGGACCC TCATGGCCTTGC-3’. PCR products were then separated by agarose gel electrophoresis using O’RangeRuler™ 50 bp DNA Ladder (Fermentas) as a length marker (Figs. **1**, **2**, and **3**) [38].

The expected size of PCR products for: a) COMT gene were Met/Met (A/A), 96 bp only; Val/Met (A/G) 114 and 96 bp; and Val/Val (G/G), 114 bp only.

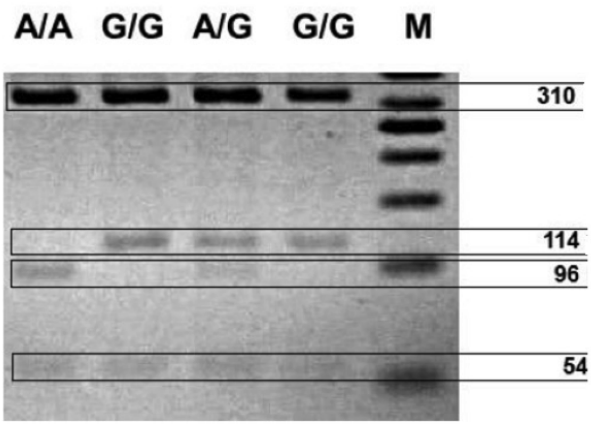

Fig. (1). Representative photo of the digested COMT PCR products.
Electrophoresis results are marked with the genotypes: Met / Met (A / A), only 96 bp; Val / Met (A / G) 114 and 96 bp; and Val / Val (G / G), only 114 bp.

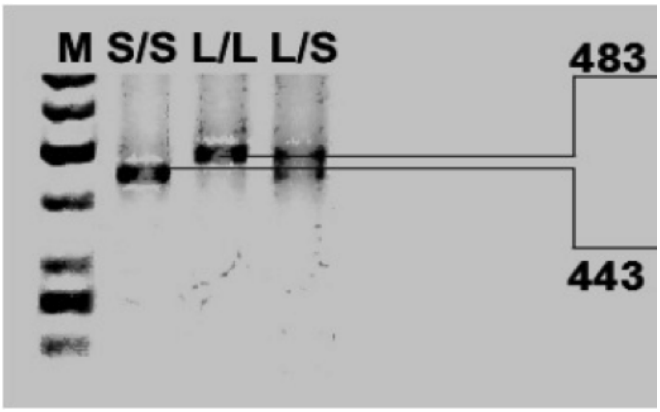

Fig. (2). Representative photo of digested DAT1 PCR products.
Electrophoresis results are marked with the genotypes: 10/10 (L/L) 483 bp only; 10/9 (L/S) 483 and 443 bp; and 9/9 (S/S) 443 bp only.

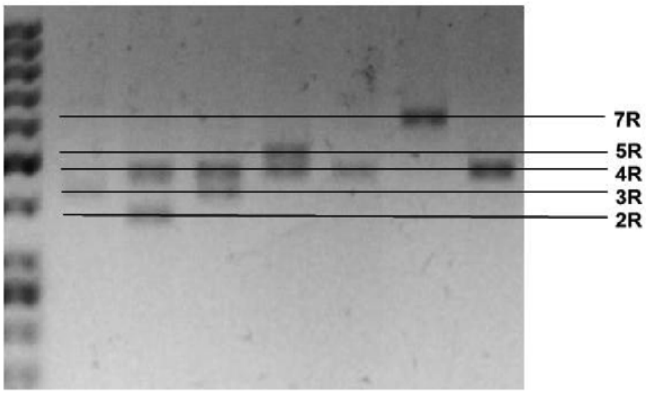

Fig. (3). Representative photo of digested DRD4 PCR products.
Representative photo of electrophoresis of seperated DRD4 PCR products depending on the genotype: LL – only 619 bp band (7R); S/S 379 bd (2R) or/and 427 bp (3R) or/and 523 bp (5R) band; L/S – 379 bd (2R) or 427 bp (3R) or 523 bp (5R) and 619 bp (7R) bands.

b) *DAT1* gene were: 10/10 (L/L) 483 bp only; 10/9 (L/S) 483 and 443 bp; and 9/9 (S/S) 443 bp only.

c) *DRD4* gene were: LL – only 619 bp band (7R); S/S 379 bd (2R) or/and 427 bp (3R) or/and 523 bp (5R) band; L/S – 379 bd (2R) or 427 bp (3R) or 523 bp (5R) and 619 bp (7R)Statistical analysis

Using the Shapiro-Wilk test, it was determined that the test group does not meet the normal distribution criteria. Statistical significance of differences between two groups was calculated using the Mann–Whitney U test, and for comparisons with three or more groups, the Kruskal–Wallis analysis of variance (ANOVA) was applied. The Least Significant Difference (LSD) Fisher test was used for post hoc analyses. The effect size was determined using Cohen's d. The multiple testing procedure was then performed to confirm the validity of the relevant results for genetic polymorphisms. After applying Bonferroni correction, results with p-value < 0,016 were considered to be significant. Statistica 10.0 used for statistical analyses Deviation from Hardy-Weinberg equilibrium was analyzed using Pearson $\chi 2$ test ($p < 0.05$) with OOoStat package for OpenOffice.org Calc and R v 2.12.0. The distribution of all three analyzed genotypes was in Hardy-Weinberg equilibrium (COMT p=0,87; DAT p=0,45; DRD4 p=0,37).

3. RESULTS

The study population consisted of 248 individuals with a diagnosis of simple obesity. The median age was 45.2 years in the study group. There were 179 women and 69 men in the study group. The results of the WCST and basic demographic factors are presented in Table **1**. There were no significant differences between women and men in age, BMI and WCST parameters.

Table **2** presents the relationships between WCST parameters, age and BMI in groups of women and men. It was revealed that in both groups, age was associated with the significantly worse performance of tests in all dimensions tested. Moreover, in the group of women, the higher BMI was associated with a significantly higher number of errors, both perseverative and non-perseverative, and a significantly lower number of responses consistent with the logical concept. Similar relationships were not observed in the group of men.

Correlation analysis of the studied COMT gene polymorphism in the group of women showed better performance of the WCST dimensions by patients with polymorphism A/A or G/A but after adopting multiple testing results, they did not maintain statistical significance (Table **3**). However, in the subgroup of all men, G/A heterozygotes were only characterized by a higher BMI (p=0.02). In the younger women's group, a higher BMI was observed among A/A of homozygous subjects and a worse WCST performance in the parameter of a number of cards needed to arrange the first category in the genotype G/G. Similar relationships were not sought among older women (Table **4**) and in subgroups of men.

The analyzed polymorphism of the *DAT1* gene in the female population revealed only non-significant differences between individual alleles. In contrast, in the male population, the carriers of the long allele (L/L and L/S) made insignificantly fewer non-perseverative errors, according to the Bonferroni correction, (Table **5**). The results obtained in subgroups of men and

Table 1. Body mass index (BMI), depression symptoms (BDI), and results on the Wisconsin Card Sorting test (WCST) in study participants. Data are presented as medians and 25th and 75th quartiles.

	Female (n = 179)	Male (n = 69)	P	Cohen's d
Age	44.5 (29.0 – 49.0)	45.0 (32.0 – 53.0)	0.11	0.22
BMI	41.6 (37.1 – 47.3)	44.5 (39,7 – 49,5)	0.80	0.03
WCST_P	11.0 (8.0 – 16.0)	9.0 (7.0 – 16.0)	0.65	0.14
WCST_NP	11.0 (7.0 – 16.0)	10.0 (5.0 – 19.0)	0.82	0.02
WCST_CLR	72.0 (58.0 – 81.0)	75,0 (52.0 – 84.0)	0.99	0.04
WCST_CC	6.0 (5.0 – 6.0)	6.0 (3.0 – 6.0)	0.15	0.19
WCST_1st	12.0 (11.0 – 15.0)	12.0 (11.0 – 19.0)	0.22	0.17

BMI, body mass index; ; WCST_P, percentage of perseverative errors; WCST_NP, percentage of nonperseverative errors; WCST_CLR, percentage of conceptual responses; WCST_CC, level of category completed; WCST_1st, number of cards needed to complete first category. Significance of differences between sexes was determined by the Mann– Whitney U test. Size effect was measured by Cohen's d method.

Table 2. R-Spearman correlations of age and BMI result with WCST scores in women and men.

	Female (n = 179)		Male (n = 69)	
	Age	**BMI**	**Age**	**BMI**
WCST_P	r= 0.20; p=0.006	r= 0.16; p=0.02	r= 0.37; p=0.001	r= -0.12; p=0.62
WCST_NP	r= 0.27; p<0.001	r= 0.19; p=0.01	r= 0.46; p<0.001	r= 0.001; p=0.99
WCST_CLR	r= -0.24; p=0.001	r= -0.15; p=0.04	r= -0.56; p<0.001	r= 0.06; p=0.62
WCST_CC	r= -0.21; p=0.01	r= -0.04; p=0.59	r= -0.45; p<0.001	r= 0.11; p=0.36
WCST_1st	r= 0.21; p=0.02	r= 0.11; p=0.14	r= 0.27; p=0.02	r= -0.21; p=0.08

BMI, body mass index; ; WCST_P, percentage of perseverative errors; WCST_NP, percentage of nonperseverative errors; WCST_CLR, percentage of conceptual responses; WCST_CC, level of category completed; WCST_1st, number of cards needed to complete first category.

Table 3. COMT polymorphisms and WCST results in subgroups pf women and men.

	Female (n = 179)				Male (n = 69)			
	G/G (n= 59)	**G/A (n= 74)**	**A/A (n= 46)**	**P**	**G/G (n=12)**	**G/A (n=44)**	**A/A (n=13)**	**P**
BMI	42.1 (38.4 – 45.5)	41.5 (36.4 – 47.5)	42.9 (37.2 – 47.9)	0.80	36.1 (31.4 – 40.5)	44.0 (39.4 – 51.2)	38.8 (30.5 – 48.3)	0.04 Post hoc G/G vs AA 0.02
WCST_P	13.5 (9.0 – 16.0)	11,0 (7.0 – 13.0)	12.0 (8.0 – 20.0)	0.05 Post hoc G/G vs A/A 0.02	9.0 (7.0 – 37.0)	9.0 (6.0 – 12.0)	9.0 (7.0 – 20.0)	0.62
WCST_NP	12.0 (8.0 – 20.5)	10.0 (7.0 – 13.0)	10.0 (8.0 – 17.0)	0.23	13.5 (8.0 – 19.0)	11.0 (5.0 – 21.0)	8.0 (6.0 – 17.0)	0,86
WCST_CLR	64.0 (42.0 – 80.5)	75.0 (66.0 – 82.0)	72.0 (49.0 – 79.0)	0.08	72.0 (27.0 – 81.0)	73.0 (58.0 – 83.0)	81.0 (33.0 – 84.0)	0,64
WCST_CC	6.0 (4.0 – 6.0)	6.0 (6.0 – 6.0)	6.0 (3.0 – 6.0)	0.05 Post hoc G/G vs AA 0.03 G/A vs AA 0.02	6.0 (0.0 – 6.0)	6.0 (3.0 – 6.0)	6.0 (5.0 – 6.0)	0,79
WCST_1st	13.0 (11.0 – 24.5)	12.0 (11.0 – 12.0)	12.0 (11.0 – 25.0)	0.03 Post hoc G/G vs AA 0.04 G/A vs AA 0.04	22.0 (12.0 – 129.0)	12.0 (11.0 – 23.0)	12.0 (11.0 – 18.0)	0,27

BMI, body mass index;WCST_P, percentage of perseverative errors; WCST_NP, percentage of nonperseverative errors; WCST_CLR, percentage of conceptual responses; WCST_CC, level of category completed; WCST_1st, number of cards needed to complete first category. Significance of differences between subgroups was determined by the Kruskal-Wallis ANOVA. Post-hoc analysis was conducted with Fisher's LSD test.

Table 4. COMT polymorphisms and WCST results in subgroups of women in age ≤45 y and > 45 y.

	Female ≤45 (n = 99)				Female >45 (n = 80)			
	G/G (n= 32)	G/A (n= 35)	A/A (n= 32)	P	G/G (n=27)	G/A (n=39)	A/A (n=14)	P
BMI	43.3 (40.8 – 46.9)	40.7 (36.5 – 44.5)	44.6 (37.2 – 50.4)	0.04 Post hoc G/G vs. G/A 0.03 AA vs. G/A 0.005	39.1 (32.8 – 42.9)	47.4 (36.2 – 57.0)	39.4 (37.2 – 43.8)	0.19
WCST_P	12.0 (7.5 – 16.0)	11.0 (7.0 – 13.0)	11.5 (8.0 – 21.0)	0.27	13.5 (10.0 – 19.0)	11.0 (6.0 – 12.0)	12.0 (7.0 – 13.0)	0.11
WCST_NP	10.5 (7.0 – 16.5)	9.5 (6.0 – 12.0)	12.0 (8.0 – 17.0)	0,.24	12,0 (8,5 – 26,0)	12,0 (8,0 – 16,0)	10.0 (8.0 – 18.0)	0.61
WCST_CLR	61.0 (51.0 – 82.5)	7.,0 (71.0 – 82.0)	72.0 (49.0 – 79.0)	0,.12	69,5 (39,5 – 75,5)	67.0 (60.0 – 82.0)	75.0 (64.0 – 84.0)	0.44
WCST_CC	6.0 (4.0 – 6.0)	6.0 (6.0 – 6.0)	6.0 (3.0 – 6.0)	0.04 Post hoc Ns.	6,0 (2,5 – 6,0)	6.0 (5.0 – 6.0)	6.0 (6.0 – 6.0)	0.49
WCST_1st	13.0 (12.0 – 38.0)	11.0 (11.0 – 12.0)	11.5 (11.0 – 13.0)	0.01 Post hoc G/G vs. G/A 0.03	11,0 (11,0 – 14,0)	12.0 (12.0 – 23.0)	21.0 (11.0 – 35.0)	0.44

BMI, body mass index; ; WCST_P, percentage of perseverative errors; WCST_NP, percentage of nonperseverative errors; WCST_CLR, percentage of conceptual responses; WCST_CC, level of category completed; WCST_1st, number of cards needed to complete first category. Significance of differences between subgroups was determined by the Kruskal-Wallis ANOVA. Post-hoc analysis was conducted with Fisher's LSD test.

Table 5. DAT polymorphisms and WCST results in subgroups of women and men.

	Female (n = 179)				Male (n = 69)			
	L/L (n= 88)	L/S (n= 72)	S/S (n= 19)	P	L/L (n=38)	L/S (n=21)	S/S (n=10)	P
BMI	41.0 (36.5 – 47.0)	41.6 (36.0 – 48.8)	40.7 (39.9 – 46.8)	0.80	43.9 (35.2 – 51,2)	41.5 (32.4 – 48.5)	40.8 (40.1 – 41.8)	0.68
WCST_P	10.0 (7.0 – 13.0)	12.0 (7.0 – 16.0)	11.0 (9.0 – 12.0)	0.06 Post hoc ns.	9.0 (7.0 – 12,0)	8.0 (5.0 – 14.0)	11.0 (8.5 – 23.5)	0.43
WCST_NP	10.0 (7.0 – 14.5)	12.0 (9.0 – 17.0)	8.0 (7.0 – 16.0)	0.08	12.0 (8.0 – 19.0)	6.5 (5.0 – 9.0)	15.5 (14.0 – 16.0)	0.04 Post hoc ns.
WCST_CLR	73.5 (62.0 – 83.0)	72.0 (57.0 – 81.0)	74.0 (57.0 – 81.0)	0.05 Post hoc Ns.	74.5 (56.5 – 82.0)	81.5 (69.0 – 85.0)	64.5 (48.0 – 73.0)	0.23
WCST_CC	6.0 (6.0 – 6.0)	6.0 (4.0 – 6.0)	6.0 (4.0 – 6.0)	0.22	6.0 (2.0 – 6.0)	6.0 (6.0 – 6.0)	4.5 (3.5 – 5.5)	0.09
WCST_1st	12.0 (11.0 – 13.0)	12.0 (11.0 – 35.0)	11.0 (11.0 – 12.0)	0.08 Post hoc L/L vs S/S 0.002 L/S vs S/S 0.01	12.5 (11.0 – 25.0)	11.5 (11.0 – 18.0)	17.5 (14.0 – 28.5)	0.33

BMI, body mass index; ; WCST_P, percentage of perseverative errors; WCST_NP, percentage of nonperseverative errors; WCST_CLR, percentage of conceptual responses; WCST_CC, level of category completed; WCST_1st, number of cards needed to complete first category. Significance of differences between subgroups was determined by the Kruskal-Wallis ANOVA. Post-hoc analysis was conducted with Fisher's LSD test.

Table 6. DAT polymorphisms and WCST results in subgroups of women in age ≤45 y and > 45 y.

	Female =<45 (n = 99)				Female >45 (n = 80)			
	L/L (n= 47)	L/S (n= 41)	S/S (n= 11)	P	L/L (n=41)	L/S (n=31)	S/S (n=8)	P
BMI	40.9 (37.2 – 44.8)	42.7 (36.2 – 48.8)	40.1 (37.2 – 41.9)	0.54	43,5 (34.1 – 52.4)	40.8 (35.5 – 47.4)	48.8 (40.2 – 57.0)	0.63
WCST_P	9.0 (7.0 – 13.0)	10.0 (7.0 – 15.0)	10.5 (9.0 – 12.0)	0.80	11.0 (7.0 – 13.0)	13.5 (9.5 – 19.0)	12.0 (8.0 – 22.0)	0.24
WCST_NP	9.0 (7.0 – 14.0)	12.0 (8.0 – 16.0)	7.0 (4.0 – 11.0)	0.09	10.5 (8.0 – 15.0)	12.5 (10.0 – 24.0)	16.0 (8.0 – 23.0)	0.09
WCST_CLR	76.5 (62.0 – 84.0)	72.0 (59.0 – 82.0)	76.0 (72.0 – 81.0)	0.67	71.5 (62.0 – 82.0)	67.0 (42.0 – 74.5)	57.0 (37.0 – 82.0)	0.21
WCST_CC	6.0 (6.0 – 6.0)	6.0 (5.0 – 6.0)	6.0 (6.0 – 6.0)	0.53	6.0 (6.0 – 6.0)	6.0 (2.0 – 6.0)	4.0 (1.0 – 6.0)	0.07 Post hoc L/L vs L/S 0.01
WCST_1st	12.0 (11.0 – 13.0)	12.0 (11.0 – 20.0)	11.0 (10.0 – 11.0)	0.04	11.0 (11.0 – 13.0)	37.5 (11.5 – 61.0)	12.0 (12.0 – 27.0)	0.006 Post hoc L/L vs L/S 0.002 L/S vs S/S 0.03

BMI, body mass index; ; WCST_P, percentage of perseverative errors; WCST_NP, percentage of nonperseverative errors; WCST_CLR, percentage of conceptual responses; WCST_CC, level of category completed; WCST_1st, number of cards needed to complete first category. Significance of differences between subgroups was determined by the Kruskal-Wallis ANOVA. Post-hoc analysis was conducted with Fisher's LSD test.

Table 7. DAT polymorphisms and WCST results in subgroups of men in age ≤45 y and > 45 y.

	Male =<45 (n = 36)			Male >45 (n = 33)			
	L/L (n=24)	L/S & S/S (n=12)	P	L/L (n=14)	L/S (n=11)	S/S (n=8)	P
BMI	39.9 (36.3 – 49.2)	41.0 (36..6 – 47.6)	0.75	43.7 (33.3 – 48.9)	44.7 (30.3 – 49.1)	40.3 33.7 – 45.9)	0.84
WCST_P	9.0 (8.0 – 12.0)	9.0 (6.0 – 12.0)	0.007	12.5 (7.0 – 20.0)	14.0 (11.0 – 27.0)	13.5 (10.0 – 31.5)	0.71
WCST_NP	10.0 (5.5 – 16.0)	8.0 (4.0 – 13.0)	0.19	20.0 (18.0 – 22.0)	12.0 (5.0 – 21.0)	16.0 (14.0 – 17.0)	0.05 Post hoc Ns.
WCST_CLR	76.0 (71.0 – 83.0)	8.,0 (73.0 – 85.0)	0.12	55.0 (33.0 – 72.0)	69.0 (26.0 – 76.0)	61.5 (39.0 – 71.5)	0.91
WCST_CC	6.0 (5.0 – 6.0)	6.0 (6.0 – 6.0)	0.49	2.5 (1.0 – 6.0)	6.0 (3.0 – 6.0)	4.0 (3.0 – 5.0)	0.11
WCST_1st	12.0 (11.0 – 21.5)	12.0 (11.0 – 20.0)	0.66	19.5 (12.0 – 30.0)	11.0 (11.0 – 31.0)	17.5 (14.0 – 37.0)	0.14

BMI, body mass index; ; WCST_P, percentage of perseverative errors; WCST_NP, percentage of nonperseverative errors; WCST_CLR, percentage of conceptual responses; WCST_CC, level of category completed; WCST_1st, number of cards needed to complete first category. Significance of differences between subgroups was determined by the Mann-Whitney U test (2 groups) and Kruskal-Wallis ANOVA (3 groups). Post-hoc analysis was conducted with Fisher's LSD test.

Table 8. DRD4 polymorphisms and WCST results in subgroups of women in age ≤45 y and > 45 y

	Female =<45 (n = 99)			Female >45 (n = 80)		
	L/L; L/S (n= 33)	S/S (n= 66)	P	L/L & L/S (n=30)	S/S (n=50)	P
BMI	40.2 (37.4 – 43.5)	42.9 (37.5 – 47.1)	0.27	44.3 (40.2 – 52.5)	43.2 (38.3 – 48.8)	0.68
WCST_P	11.0 (7.0 – 13.5)	9.0 (7.0 – 13.0)	0.07	12.0 (9.0 – 13.0)	13.0 (9.0 – 17.0)	0.09
WCST_NP	9.0 (6.0 – 14.0)	9.0 (7.0 – 14.0)	0.77	12.0 (9.0 – 20.0)	11.0 (8.0 – 18.0)	0.13
WCST_CLR	79.0 (60.5 – 84.5)	76.0 (63.0 – 84.0)	0.79	72.0 (60.0 – 81.0)	68.0 (53.0 – 82.0)	0.15
WCST_CC	6.0 (6.0 – 6.0)	6.0 (6.0 – 6.0)	0.47	6.0 (5.0 – 6.0)	6.0 (4.0 – 6.0)	0.10
WCST_1st	12.0 (11.0 – 16.0)	12.0 (11.0 – 13.0)	0.57	13.0 (11.0 – 28.0)	12.0 (11.0 – 30.0)	0.003

BMI, body mass index; ; WCST_P, percentage of perseverative errors; WCST_NP, percentage of nonperseverative errors; WCST_CLR, percentage of conceptual responses; WCST_CC, level of category completed; WCST_1st, number of cards needed to complete first category. Significance of differences between sexes was determined by the Mann– Whitney U test.

Table 9. DRD4 polymorphisms and WCST results in subgroups of women in age ≤45 y and > 45 y.

	Male =<45 (n = 36)			Male >45 (n = 33)		
	L/L; L/S (n=12)	S/S (n=24)	P	L/L & L/S (n=17)	S/S (n=16)	P
BMI	44.1 (38.2 – 52.5)	40.0 (3.,8 – 43.8)	0.13	44.7 (31.1 – 51.5)	41.9 (33.6 – 47.4)	0.68
WCST_P	9.5 (5.0 – 12.0)	9.0 (6.0 – 10.0)	0.82	12.0 (7.0 – 15.0)	23.5 (10.0 – 36.0)	0.06
WCST_NP	7.5 (4.5 – 11.5)	10.0 (4.0 – 19.0)	0.52	15.0 (9.0 – 18.0)	19.0 (14.5 – 21.5)	0.06
WCST_CLR	83.0 (73.5 – 85.0)	76.0 (73.0 – 86.0)	0.54	69.0 (52.0 – 76.0)	36.5 (26.5 – 67.5)	0.006
WCST_CC	6.0 (6.0 – 6.0)	6.0 (6.0 – 6.0)	0.90	5.0 (4.0 – 6.0)	2.5 (1.0 – 5.5)	0.04
WCST_1st	12.5 (10.5 – 20.5)	12.0 (11.0 – 20.0)	0.98	12.0 (11.0 – 24.0)	22.0 (11.5 – 53.5)	0.12

BMI, body mass index; ; WCST_P, percentage of perseverative errors; WCST_NP, percentage of nonperseverative errors; WCST_CLR, percentage of conceptual responses; WCST_CC, level of category completed; WCST_1st, number of cards needed to complete first category. Significance of differences between sexes was determined by the Mann– Whitney U test.

women of different ages showed significant differences in the population of older women where better results were associated with allele L (Table **6** and Table **7**).

Due to the small number of people with the L/L allele (5 of 249), people with L/L and L/S alleles were connected into one group. In the subgroups of both women and men, there were no significant associations excepting correlation L allele with a nearly significantly higher BMI in men (p=0.02). No other significant dependencies were found. However, in the subgroups of older women and men, the correlations obtained were divergent. Among women, the S allele was associated with a significantly better result in terms of

Table 10. Linear regression model coefficients on WCST results.

	WCST_P			WCST_NP			WCST_CLR			WCST_CC			WCST_1st		
	SS	F	p	SS	F	p	SS	F	p	SS	F	p	SS	F	p
Gender	7.15	0.13	0.72	27.1	0.38	0.53	59.8	0.14	0.70	11.9	2.89	0.04	2952	3.96	0.04
Age	57.1	1.01	0.31	408	5.82	0.01	2457	6.09	0.01	9.1	2.32	0.12	7407	10.0	0.001
BMI	5.98	0.12	0.73	210	2.99	0.08	139.7	0.34	0.55	1.04	0.26	0.60	210	0.25	0.61
DAT1	79.7	0.78	0.45	46.4	0.29	0.74	163	0.20	0.81	2.1	0.28	0.75	4014	2.73	0.06
COMT	344	3.07	0.04	372	2.42	0.09	*3357*	*4.13*	*0.01*	18.5	2.36	0.09	4591	2.95	0.04
DRD4	238	2.21	0.11	92.2	0.68	0.50	1456	1.89	0.15	2.02	0.28	0.74	100	0.07	0.92

BMI, body mass index; ; WCST_P, percentage of perseverative errors; WCST_NP, percentage of nonperseverative errors; WCST_CLR, percentage of conceptual responses; WCST_CC, level of category completed; WCST_1st, number of cards needed to complete first category.

the cards needed to form the first category (p=0.003). Among men, patients with S / S alleles achieved lower conceptual level response (p=0.006) and composed a fewer number of categories (p=0.04 – nonsignificant due to Bonferroni correction) (Table **8** and Table **9**).

The analysis performed on the linear regression model indicated the coefficient of gender to be significant predictor of categories completed (p=0.04) and number of cards needed to complete first category (p=0.04), age to be significant predictor of non-perseverative errors (p=0.01), conceptual level response (p=0.01) and number needed to complete first category (p=0.001), and also pointed to COMT as a significant predictor of perseverative errors (p=0.04), conceptual levels response (p=0.01) and number of cards needed to complete first category (p=0.04).

4. DISCUSSION

Dopamine is a key neurotransmitter in the brain, involved in motor and limbic functions. Experimental studies showed that DA alterations within mesocorticolimbic areas may contribute to cognitive deficits [39]. Changes in dopaminergic neurotransmission may be noticed mostly within frontal lobes and basal ganglia. Both subcortical and cortical areas are connected, therefore cognitive deficits may be linked to the alterations within those areas [39,40,41]. In this study, we have observed that gene polymorphisms which are expressed mainly in frontal lobes (*COMT*Val158Met, *DRD4*) and subcortical regions (*DAT1*) showed some associations with WCST results, thus executive functions.

According to Table **2**, the amount of perseverative and non-perseverative errors positively correlated with BMI values in a group of women. This is consistent with previous studies performed on obese subjects [42,43]. However, we have not observed the same changes in males, probably due to the very small amount of participants. More importantly, the regression model did not confirm the importance of BMI as a predictor of prefrontal cortex dysfunction in the whole group.

Changing one's behavior in order to achieve goals (or to complete the category in WCST) requires executive functions such as executive control [44]. In the situation when the rule changes, the participant has to inhibit their usual response and employs a new one. Both actions require inhibition and disinhibition. A higher number of perseverative errors indicates inefficient inhibitory control and disturbances within set-shifting [32]. Both dysfunctions may increase the risk of obesity, supporting the inhibitory control theory of obesity [45,46]. Similarly, patients with ADHD demonstrate dysfunction in inhibitory control, which is controlled by dorsolateral prefrontal cortex [47,48]. The neuroimaging study of Batterink *et al*., showed that obese subjects had significantly lower activation in this region of PFC, in comparison to lean individuals in the task based on inhibiting the response to food images [49].

Both men and women showed significant correlations between WCST dimensions and age, which may result from the age-associated frontal lobe impairments [50].

Subsequent tables demonstrate relations between dopaminergic gene polymorphisms and WCST scores. Regarding *COMT*Val158Met, we have observed significant results of ANOVA (Table **3**) in the group of females. At the same time, the regression model confirmed that COMT is a significant predictor of WCST parameters related to prefrontal cortex function.

COMT enzyme regulates DA catabolism in the synaptic cleft, inhibiting its biological function and is mostly translated in the PFC than in subcortical regions. The *COMT* gene is located at 22q11.2 chromosome, and the most common is the single nucleotide polymorphism (SNP) *COMT*Val158Met (rs4680) which alters the enzyme's activity [51,52]. Carriers of M*et a*llele show lower enzyme activity, resulting in higher DA availability in the PFC. Conversely, subjects possessing Val allele tend to have higher COMT activity leading to reduced dopaminergic signaling [53,54].

Results included in Table **3**, which (after applying the multiple testing) are on the verge of significance, indicate, that Val homozygotes made more perseverative errors in comparison to Met carriers and

needed more cards to complete the first category. Poorer cognitive functioning may stem from the lower dopaminergic signaling due to Val/Val polymorphism. This is in accordance with findings from the studies performed on schizophrenic patients and healthy individuals [55.56,57,58]. In the group of females, the best cognitive performance was achieved by heterozygotes. This supports the notion for DA's inverted U-shaped effect on cognitive functions. In PFC, the relationship between DA and cognitive functions acts like inverted-U shape, hence surfeit or dopamine depletion may impair cognitive processing [59].

Table **4** presents significant associations, after applying the Bonferroni correction, between WCST dimensions and genotype in younger females but not in older participants. The loss of brain dopamine availability with the following cognitive decline has been observed in many studies [60,61]. Lindenberger *et al*. proposed "resource modulation hypothesis", which is based on the changes within the dopaminergic system during the life span [61]. The constant age-related loss of the dopaminergic system elements within the brain may multiply the effect of genes modulating dopaminergic neurotransmission, like COMT gene, hence greatly affect executive functioning and working memory [62]. Such a phenomenon may stem from the inverted-U shaped effect of dopamine activity on PFC. We have not observed this effect in our participants, putatively due to the small amount of participants.

COMTVal158Met have been reported to have sex-related dimorphic effects on cognition [58.63,64,65]. We did not observe any significant correlations between COMT genotype and executive functions in the male subgroup. However, in the study of Hupfeld *et al*. [58], older males (>85 years old) expressed stronger associations between COMT polymorphisms and cognition than females. The possible explanation is that estrogen exerts downregulating effect on COMT mRNA. Thus, women with higher estrogen levels have lower COMT activity and greater dopaminergic signaling within fronto-subcortical loops. After menopause, this interaction may be diminished or disappear, leading to reduced differences between men and women [65]. Moreover, the study on post-mortem brain tissue revealed higher COMT activity in PFC in males than females [53].

We have observed associations between *DAT1* gene polymorphisms and WCST performance. In our sample, DAT1 polymorphisms did not show significant correlations with every WCST dimension, but some post hoc analysis remained relevant. Nonetheless, we have obtained some results which support earlier findings indicating that lower dopaminergic transmission may account for poorer cognitive performance.

The human dopamine active transporter (DAT) regulates dopamine concentration in the DA synapse by re-uptaking the neurotransmitter which was released into the synaptic cleft [66]. DAT is mostly distributed in the basal ganglia of the human brain. The *DAT1* (*SLC6A3*) is localized on chromosome 5p15.3 and has a 40-bp variable number tandem repeat (VNTR) polymorphism within its 3′ untranslated region. The A9 allele is putatively associated with reduced DAT protein expression, leading to higher levels of dopamine in the striatum and thus augmented ventral striatal activity [67,68]. Ten repeat allele codes higher overall DAT concentration, resulting in greater DA reuptake and hence reduces synaptic dopamine availability [69].

In Table **5**, we have observed the differences between males and females in WCST performance. Group of women did not show any significant correlations between *DAT1* alleles and WCST dimensions, however, there is a trend, confirmed in post hoc analysis, towards significance indicating that 9R homozygotes may show better cognitive results in comparison to 10R carriers. Males homozygous to 9R showed a non-significantly greater number of non-perseverative errors, in contrast to 10R carriers. Non-perseverative errors in WCST seem to be the combination of different types of errors: efficient and distraction errors. Efficient errors are needed to successfully perform the task, as the sign of intentional shifting toward the wrong concepts in order to receive disconfirming feedback. Based on the received data, the subject may adjust the strategy to sort the cards correctly [70,71]. Distraction errors seem to be random failures to maintain set, which ensue from fluctuation while making a choice during sorting the cards [70]. Those arguments suggest low specificity of WCST and show that more specific tests are needed for better assessment of the set-shifting errors [70].

Subsequently, we have analyzed cognitive performance in the groups of females and males, by dividing them by their age. Younger women (< 45 years old) did not show any correlations between WCST parameters and gene polymorphisms. However, in the older group, we observed significant differences between heterozygotes and homozygotes regarding the number of cards needed to complete the 1st category in WCST (WCST 1st) with heterozygotes showing the worst performance. The male subgroup showed significant correlations while making perseverative errors (males < 45 y.o.) and non-perseverative errors (males > 45 years old). In both cases, 10R homozygotez scored worse in WCST, which is consistent with findings from the literature [72,73].

Studies have reported the influence of DAT availability on cognitive performance [28,74,75]. A recent study of Chung *et al*. [28] performed on patients suffering from Parkinson's disease manifested that lower DAT availability was associated with poorer working memory and executive functions. Also in our study, homozygotes to 10R allele, which is associated with diminished DAT expression, showed worse scores in WCST - a proxy for frontal lobes functions.

An experimental study by Ralph *et al*. [75] showed that knockout mice demonstrated more repetitive behavior, which implies making more perseverative errors and indicates worse cognitive flexibility. Moreover, in the study of Hsieh *et al*. [74], the negative correlation between DAT striatal concentration and the amount of perseverative errors in WCST was

observed. In our study, young 10/10 males made significantly more perseverative errors than 9R carriers, which is consistent with other findings suggesting poorer performance in this dimension in obese individuals [76,77].

Estrogen regulates dopamine transmission, thus sex differences in cognitive function between males and females may result from the sex hormones [78,79]. Estradiol may putatively reverse DAT function, promoting the efflux of dopamine through the DAT, thus causing higher dopaminergic signaling within subcortical regions [80]. In our study, the amount of perseverative and non-perseverative errors significantly correlated with 10/10 alleles in males, but not in females. One possible explanation is that women have greater dopaminergic signaling than men, even while possessing polymorphisms responsible for lower dopaminergic signaling. Whereas the factors differentiating men and women in terms of cognition are very numerous and many of them may be more important than the mechanism postulated above.

The human dopamine receptor D4 is encoded by *DRD4* gene and is localized in cortical and subcortical regions; showing higher concentration within PFC, amygdala or hippocampus, and limited expression in striatal regions [81,82]. We examined the 48-base pair exon 3 VNTR polymorphism of *DRD4*. Alleles variants may range from 2R to 11 R. The *DRD4* 7R variant encodes a dopamine receptor with a weaker inhibitory signal to cyclic adenosine monophosphate (cAMP) in comparison to shorter forms, indicating the hypo-functionality of the receptor [83,84]. Literature shows evidence of the association between *DRD4* polymorphisms and cognition [85,86,87,88]. Moreover, allele 7R of *DRD4* is strongly associated with ADHD – a disease characterized by cognitive deficits, including inhibitory control, working memory, and attention [89,90,91].

Results of our study did not demonstrate any correlations between *DRD4* alleles in subgroups of men and women. However, significant associations occurred when we divided the groups by age. In the group of older women, L allele carriers showed better cognitive performance in WCST 1st, indicating that greater dopaminergic signaling resulting from this polymorphism may correlate with better executive performance. These results may stem from the inverted-U shape effect of dopamine. The study of Heinzel *et al*. [92] demonstrated that in the state of intermediate DA availability, determined by *COMT*Val158Met, S carriers showed optimal PFC processing in Go-No-Go test. In the state of lower dopaminergic transmission, L allele carriers performed worse during the test. Moreover, this study yielded interesting results indicating that COMT x DRD4 epistatic effect may significantly impact response inhibition behavior – where disturbances are putatively involved in the pathogenesis of obesity. Unfortunately, in our study, we did not scrutinize the epistatic effect between the genotypes. Due to the small sample, we had to combine heterozygotes with homozygotes, therefore our results may be difficult to interpret regarding inverted-U shape dependency of DA gene polymorphisms on executive functions. This may be the explanation of divergent results showing that males homozygous to S allele showed better cognitive performance in WCST.

During aging, brain structures decline which may magnify genetic effects on cognitive performance. Studies have observed the effects of COMT genotype on cognitive performance in older individuals, which may stem from the non-linear effect of DA on PFC [61,62]. In our study, significant differences between WCST and *DRD4* polymorphism were observed in older patients, which may also be the result of age-associated magnification of *DRD4* polymorphism.

Studies suggest that in order to perform WCST efficiently, not only PFC but also different parts of brain areas are involved, like parietal lobes areas, temporo-parietal association cortex, visual cortices, parahippocampal areas or basal ganglia.[35, 93]

*DAT1*and *DRDR4* are expressed in subcortical areas, and according to our results, they are involved in the WCST performance. It has been noted, that the activity of dopaminergic neurons in the ventral tegmental area may modulate the PFC activity [94]. Thus, we assume that the dopaminergic gene which is mostly expressed in the subcortical areas (like *DAT1*or *DRD4*) may influence the functioning of different brain areas responsible for cognitive processes.

CONCLUSION

In conclusion, the presented results suggest that the prefrontal cortex functioning in the studied population shows dependence on dopaminergic transmission similar to inverted-U shape characteristic. Differences in the obtained WCST results, considering the division into age groups and groups with different gender, may suggest an important role of sex hormones in the regulation of cognitive functions dependent on the prefrontal cortex. These conclusions need confirmation in more numerous subgroups with a simultaneous assessment of sex hormone regulation.

LIST OF ABBREVIATIONS

ADHD	=	Attention deficit hyperactivity disorder
ANOVA	=	Analysis of variance
BMI	=	Body mass index
cAMP	=	Cyclic adenosine monophosphate
COMT	=	Catechol-O-methyltransferase
DA	=	Dopamine
DAT1	=	Dopamine transporter type 1
DRD4	=	Dopamine receptor D4
EDTA	=	Acidum edeticum
LSD	=	Least Significant Difference test

EF	=	Executive functions
PFC	=	Prefrontal cortex
SNP	=	Single nucleotide polymorphism
TMT	=	Trial making test
VNTR	=	Variable number of tandem repeats
WCST	=	1st – number of trials required to complete the first category
CLR	=	Conceptual level response
WCST	=	Wisconsin Card Sorting Test
WCST_CC	=	Number of correctly completed categories
WCST_NP	=	Percentage of non-perseverative errors
WCST_P	=	Perseverative error percentage

CONSENT FOR PUBLICATION

Not applicable.

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None.

CONFLICT OF INTEREST

The authors declare no conflict of interest, financial or otherwise.

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AUTHOR CONTRIBUTIONS

A. Borkowska, R.Junik, and A.Tretyn conceived the idea for the study. M.Bieliński and M.Jaracz contributed to the design of the research. M.Bieliński, M.Sikora, M.Jaracz, N.Lesiewska, M.Tomaszewska, and A.Kamińska were involved in data collection. M.Bieliński, M.Jaracz, N.Lesiewska, and A.Borkowska analyzed the data. M.Bieliński and N.Lesiewska wrote the manuscript. A.Borkowska 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.

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The Association Between Affective Temperament Traits and Dopamine Genes in Obese Population

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Abstract: Studies indicate the heritable nature of affective temperament, which shows personality traits predisposing to the development of mental disorders. Dopaminergic gene polymorphisms such as *DRD4*, *COMT*Val158Met, and *DAT1* have been linked to affective disorders in obesity. Due to possible correlation between the aforementioned polymorphisms and the affective temperament, the aim of our research was to investigate this connection in an obese population. The study enrolled 245 obese patients (178 females; 67 males). The affective temperament was assessed using the Temperament Evaluation of Memphis, Pisa, Paris, and San Diego autoquestionnaire (TEMPS-A). Genetic polymorphisms of *DAT1*, *COMT*Val158Met and *DRD4* were collected from peripheral blood sample and determined using a polymerase chain reaction (PCR). Only in COMT polymorphisms, the cyclothymic and irritable dimensions were significantly associated with Met/Val carriers ($p = 0.04$; $p = 0.01$). Another interesting finding was the correlation between the affective temperament and age in men and women. We assume that dopamine transmission in heterozygotes of COMT may determine the role of the affective temperament in obese persons. Dopaminergic transmission modulated by COMT may be responsible for a greater temperament expression in obese individuals. To our knowledge, this is the first study describing the role of affective temperament in the obese population, but more research is needed in this regard.

Keywords: dopaminergic gene polymorphisms; affective temperament; obesity

1. Introduction

Previous research devoted to eating disorders, mainly related to anorexia and bulimia, indicated the possibility of specific personality traits related to both the predisposition to the disease and those affecting the course and clinical picture of the disease [1]. The psychological aspects of predisposition to obesity are mostly: disorders of the self-regulation mechanism, beliefs and expectations of the individual, personality traits, difficulties in coping with stress and experienced emotions [2]. Recent psychiatric studies suggest that there is a link between obesity and mood disorders. The association between obesity and depression occurred in childhood. Previous research indicated that the symptoms of eating disorders are common and that patients with bipolar disorder are more obese than the control group [3–5]. The results indicate that the symptoms of eating disorders are common and that patients with bipolar disorder are more obese than the control group [6,7]. Along with the broadening of the limits of diagnostic criteria for bipolar disorder (BD) over the last years, research has pointed to

the high prevalence of less severe forms of BDs, in particular hypomania, among obese patients [8]. Dopamine might be a factor linking obesity with mood disorders, especially given that maladaptive changes in dopaminergic transmission have been observed in obesity and [9–11].

Yokum et al. (2015) tested the multilocus genetic composite risk score—a proxy for dopaminergic signaling—and future changes in BMI values. The results of their study revealed that *DRD4*, *COMT*Val158Met and *DAT1* polymorphisms, putatively associated with a greater DA signaling capacity, were linked to greater increases in the BMI; hence the future weight gain [12].

According to the regulatory theory, the temperament is the basic, relatively permanent character traits that manifests in the formal specifics of behavior. These features are already present in early childhood and are common to humans and animals. Being originally determined by innate physiological mechanisms, temperament may change under the influence of puberty, aging and certain environmental factors. In their work, Serafini et al. (2015) showed that unpleasant events, inter alia: sexual abuse, physical abuse, child maltreatment or domestic violence, were associated with greater depression and suicidality in adolescents. It is worth noting that the type of events, as well as the frequency and the timing of maltreatment, may influence the risk of psychiatric disorders, including suicidal behavior, due to the disruption in the brain development connected to cognitive, social or emotional functioning [13].

According to Arnold Buss and Robert Plomin (1984), temperament is a set of inherited personality traits that are revealed in early childhood. The temperament understood in this way is the basis for shaping and developing personality [14]. According to the assumptions of modern psychiatry, temperament is considered a personality aspect that takes into account the constant behavior of the individual, predicts mood changes and is strongly genetically conditioned [15–17].

An important researcher in the field of psychiatry, Emil Kraepelin, believed that a depressive temperament, and a manic, irritable and cyclothymic temperament is not only represented by affective predispositions, but also by subclinical variations of manic and depressive disorders. Akiskal et al. distinguished four types of affective temperament: depressive, manic, irritable and cyclothymic. In later studies, manic temperament was changed to hyperthymic temperament, and anxiety temperament was added [18–20]. The conceptualization of these five types of temperament has led to the creation of a TEMPS psychometric tool (Temperament Evaluation of Memphis, Pisa, Paris and San Diego). In studies utilizing this tool, obese patients showed significantly higher results in cyclothymic, irritable and anxious temperaments compared to the control group [21]. Assuming that the cyclothymic temperament is part of the mild spectrum of BD, these results are consistent with previous studies suggesting a higher incidence of bipolar symptoms in people with obesity [8].

The relationship between temperamental traits in Cloninger's concept (Temperament and Character Inventory—TCI) and gene polymorphism for the serotonergic and dopaminergic systems was also found. Research is still under way to determine the role of genes in the regulation and emergence of bipolarity and affective temperament [22]. So far, in obesity, this type of research is scarce. Our previous study showed a significant contribution of the SERT gene in the regulation of temperament in the obese population [23].

There are few studies in the literature describing the connection between polymorphisms of the dopaminergic system genes with personality traits, character or temperament. Thus, the aim of this project is to determine the possible role of dopaminergic pathways in the regulation of the affective temperament in the obese population. In order to accomplish our objects, we formulated the following hypotheses:

1. Individuals with higher BMI values will have greater scores in cyclothymic, anxious and irritable temperaments, which are associated with the predisposition to psychiatric comorbidities.

2. A lower dopaminergic transmission modulated by the following gene polymorphisms: *COMT*Val158Met, *DRD4* and *DAT1,* will be associated with a higher BMI and more pronounced cyclothymic, anxious and irritable dimensions.

2. Results

Basic demographic data and TEMPS-A dimensions in a group of women and men are shown in Table 1. There were significant differences only in terms of more depressed and irritable dimensions in the group of men.

Table 1. Age, body mass index (BMI) and results on the TEMPS-A scale in study participants. Data are presented as medians, and 25th and 75th quartiles.

	Female (n = 178)	Male (n = 67)	P	Cohen's d
Age	41 (36.0–47.0)	42 (34.0–48.5)	0.11	0.24
BMI	40.7 (36.3–47.0)	41.4 (35.2–48.5)	0.8	0.03
TEMPS_D	0.38 (0.28–0.52)	0.43 (0.24–0.43)	0.04	0.36
TEMPS_C	0.36 (0.24–0.52)	0.47 (0.23–0.62)	0.09	0.29
TEMPS_H	0.52 (0.35–0.62)	0.52 (0.38–0.64)	0.53	0.1
TEMPS_I	0.14 (0.05–0.28)	0.23 (0.09–0.33)	0.001	0.42
TEMPS_A	0.33 (0.24–0.55)	0.35 (0.17–0.51)	0.12	0.18

BMI, body mass index; TEMPS_D—depressive subscale of TEMPS-A; TEMPS_C—cyclothymic subscale of TEMPS-A; hyperthymic subscale of TEMPS-A; TEMPS_I—irritable subscale of TEMPS-A; TEMPS_A—anxious subscale of TEMPS-A. Significance of differences between sexes was determined by the Mann—Whitney U test. Size effect was measured by Cohen's d method.

Table 2 shows the analysis of associations between the temperamental dimensions (according to TEMPS-A) and both the age and BMI. Our results revealed, that in the group of women, a greater age significantly correlated with more expressed dimensions of depression and anxiety. Regarding the BMI, we observed its positive correlation with a greater expression of the hyperthymic temperament and a smaller cyclothymia. On the other hand, in the group of men, there was a negative correlation between age and cyclothymia. In this group, the dimensions of cyclothymia and irritability were significantly more pronounced, as the BMI values increased. A partial Kendall's regression in the group of women showed the significance of the relationship between the age and depressive temperament, the age and anxiety temperament as well as between the BMI and cyclothymic temperament. On the other hand, in the group of men, the significance was confirmed for the BMI and cyclothymic temperament.

When analyzing the correlations of the studied COMT gene polymorphisms in the subgroups of both sexes (Table 3), no significant relationships were found. Thus, we performed an ANOVA for the entire group, and then conducted a post hoc analysis only for significant results for the ANOVA, which revealed a significantly greater expression of cyclothymia in the heterozygote subgroup. Similarly, the irritability was more pronounced in the heterozygous group.

A multiple testing procedure was then performed to confirm the validity of the relevant results. After applying the Bonferroni correction, it was confirmed that the still results for the COMT gene alleles and TEMPS-A cyclothymic (p = 0.01) and irritable (p = 0.01) dimensions are considered to be significant.

According to Table 4, the analyses carried out for the *DAT1* polymorphism did not show any significant relationships of temperament dimensions according to TEMPS-A.

Table 2. R-Spearman correlations of the age and BMI result with the TEMPS scores in women and men. Partial Kendall regression for significant correlations.

	Female (n = 178)		**Male (n = 67)**	
	Age	**BMI**	**Age**	**BMI**
TEMPS_D	r = 0.21 p = 0.004 Par. Kendall's tau Tau = -2.74; p = 0.006	r = −0.14 p = 0.06	r = −0.05 p = 0.68	r = 0.06 p = 0.63
TEMPS_C	r = −0.06 p = 0.42	r = −0.16 p = 0.03 Par. Kendall's tau Tau = −0.15; p = 0.002	r = −0.26 p = 0.03 Par. Kendall's tau Tau = −0.01; p = 0.44	r = 0.33 p = 0.006 Par. Kendall's tau Tau = −0,24; p = 0.003
TEMPS_H	r = −0.09 p = 0.23	r = 0.16 p = 0.03 Par. Kendall's tau Tau = 0.01; p = 0.37	r = 0.09 p = 0.46	r = −0.09 p = 0.47
TEMPS_I	r = 0.004 p = 0.95	r = −0.07 p = 0.35	r = −0.12 p = 0.33	r = 0.31 p = 0.01 Par. Kendall's tau Tau = −0.13; p = 0.05
TEMPS_A	r = 0.16 p = 0.03 Par. Kendall's tau Tau = −0.09; p = 0.03	r = −0.11 p = 0.14	r = −0.11 p = 0.37	r = 0.07 p = 0.57

BMI, body mass index; TEMPS_D—depressive subscale of TEMPS-A; TEMPS_C—cyclothymic subscale of TEMPS-A; TEMPS_H—hyperthymic subscale of TEMPS-A; TEMPS_I—irritable subscale of TEMPS-A; TEMPS_A—anxious subscale of TEMPS-A. Par. Kendall's tau—partial Kendall's tau. Bold values indicate statistical significance.

Table 3. COMT polymorphisms and TEMPS results in study group.

	All Group (n = 245)				
	G/G (n = 64)	**G/A (n = 120)**	**A/A (n = 61)**		***p***
BMI	40.9 (36.7–44.3)	42,5 (36.5–49.0)	42,4 (37.0–48.1)		0.52
TEMPS_D	0.36 (0.28–0.42)	0.42 (0.28–0.52)	0.38 (0.28–0.43)		0.36
TEMPS_C	0.28 (0.16–0.47)	0.47 (0.24–0.64)	0.38 (0.23–0.52)	0.04	Post-hoc G/G vs G/A p = 0.014 G/A vs A/A ns G/Avs AA na
TEMPS_H	0.57 (0.50–0.67)	0.47 (0.28–0.61)	0.57 (0.38–0.57)		0.07
TEMPS_I	0.09 (0.04–0.16)	0.26 (0.09–0.33)	0.09 (0.05–0.24)	0.01	Post-hoc G/G vs G/A p = 0.01 G/A vs A/A ns G/Avs AA ns
TEMPS_A	0,32 (0.20–0.52)	0,35 (0.22–0.59)	0.32 (0.24–0.52)		0.52

BMI, body mass index; TEMPS_D—depressive subscale of TEMPS-A; TEMPS_C—cyclothymic subscale of TEMPS-A; TEMPS_H—hyperthymic subscale of TEMPS-A; TEMPS_I—irritable subscale of TEMPS-A; TEMPS_A—anxious subscale of TEMPS-A. Significance of differences between subgroups was determined by the Kruskal-Wallis ANOVA. Post-hoc analysis was conducted with Fisher's NIR test.

Table 4. DAT polymorphisms and TEMPS-A scale results in study group.

	All Group (n =245)			
	L/L (n = 117)	**L/S (n = 103)**	**S/S (n = 25)**	***p***
BMI	41.2 (36.2–48.9)	41.6 (35.8–48.5)	40.7 (39.9–46.8)	0.9
TEMPS_D	0.42 (0.28–0.52)	0.38 (0.28–0.47)	0.38 (0.28–0.47)	0.71
TEMPS_C	0.38 (0.24–0.62)	0.38 (0.23–0.57)	0.33 (0.29–0.48)	0.86
TEMPS_H	0.52 (0.36–0.61)	0.52 (0.38–0.62)	0.57 (0.38–0.62)	0.87
TEMPS_I	0.19 (0.07–0.33)	0.14 (0.05–0.28)	0.09 (0.04–0.29)	0.23
TEMPS_A	0.32 (0.21–0.52)	0.33 (0.24–0.52)	0.44 (0.28–0.59)	0.41

BMI, body mass index; TEMPS_D—depressive subscale of TEMPS-A; TEMPS_C—cyclothymic subscale of TEMPS-A; TEMPS_H—hyperthymic subscale of TEMPS-A; TEMPS_I—irritable subscale of TEMPS-A; TEMPS_A—anxious subscale of TEMPS-A. Significance of differences between subgroups was determined by the Kruskal-Wallis ANOVA.

Due to a small group of *DRD4* L/L carriers, we combined groups of individuals with L/L and L/S together, tagged them as L-carriers, and performed proper calculations. Nevertheless, as shown in Table 5, the obtained results regarding the analysis of the dependencies for DRD4 polymorphisms did not show any significant associations, in the examined group of obese subjects.

Table 5. DRD4 polymorphisms and TEMPS-A results in subgroups of women and men.

	All Group (n = 245)		
	L/L; L/S (n = 84)	**S/S 114 (n = 161)**	p
BMI	42.9 (38.5–49.0)	41.8 (37.2–47.1)	0.21
TEMPS_D	0.4 (0.28–0.47)	0.33 (0.28–0.47)	0.25
TEMPS_C	0.38 (0.24–0.61)	0.47 (0.23–0.57)	0.64
TEMPS_H	0.47 (0.35–0.59)	0.19 (0.05–0.28)	0.15
TEMPS_I	0.16 (0.05–0.33)	0.19 (0.20–0.55)	0.27
TEMPS_A	0.32 (0.24–0.47)	0.35 (0.20–0.54)	0.75

BMI, body mass index; TEMPS_D—depressive subscale of TEMPS-A; TEMPS_C—cyclothymic subscale of TEMPS-A; TEMPS_H—hyperthymic subscale of TEMPS-A; TEMPS_I—irritable subscale of TEMPS-A; TEMPS_A—anxious subscale of TEMPS-A. Significance of differences between subgroups was determined by the Kruskal-Wallis ANOVA.

After making calculations of one-dimensional analyses on TEMPS-A (Table 6), we confirmed the significant interaction effect for the gender and following temperaments: depressive, cyclothymic and irritable; for the BMI and anxious temperament; and for *COMT* Val158Met and both the cyclothymic and irritable temperament. However, we did not observe any significance for the age and other examined polymorphisms (Table 6).

Table 6. Analyses of unidimensional interaction effects for TEMPS-A temperaments subscales.

	TEMPS-D			**TEMPS-C**			**TEMPS-H**			**TEMPS-I**			**TEMPS-A**		
	SS	**F**	p	**SS**	**F**	p	**SS**	**F**	p	**SS**	**F**	p	**SS**	**F**	p
Gender	0.15	5.3	0.02	0.23	4.6	0.03	0.01	0.36	0.54	0.18	6.1	0.01	0.04	0.94	0.33
Age	2.08	1.38	0.06	2.07	0.68	0.94	2.07	1.01	0.46	1.89	1.19	0.20	3.03	1.17	0.22
BMI	0.11	0.78	0.65	0.35	4.7	0.11	0.06	0.20	0.96	0.37	4.9	0.10	0.24	17.1	0.01
DAT1	0.02	0.38	0.68	0.22	0.22	0.79	0.007	0.1	0.90	0.09	1.53	0.21	0.05	0.52	0.59
COMT	0.07	1.49	0.22	0.32	3.2	0.04	0.22	2.9	0.05	0.20	3.4	0.03	0.10	1.07	0.34
DRD4	0.02	0.49	0.61	0.04	0.39	0.67	0.07	1.08	0.34	0.07	1.36	0.35	0.01	0.11	0.89

One-dimensional analysis of significance (ANOVA) F-test based on SS.

The Wald statistic in the logistic regression model indicated the coefficient of gender to be a significant predictor of the TEMPS-D results, and the *COMT* polymorphism to be a significant predictor of the TEMPS-H and TEMPS-I results (Table 7). These test results for *COMT* in predicting TEMPS-C and TEMPS-D, and for *DAT1* in predicting TEMPS-I, remained in the trend.

Table 7. Logistic regression model coefficients on TEMPS-A temperaments subscales.

	TEMPS-D						
	B	**S.E.**	**Wald**	**df**	***p***	**95%C.I. Lower**	**95%C.I. Upper**
Gender	0.164	0.057	8.05	1	0.004	0.278	0.05
Age	0.003	0.004	0.69	1	0.4	0.011	−0.004
BMI	0.00008	0.006	0.01	1	0.89	0.013	−0.11
DAT1	0.036	0.06	0.37	2	0.82	0.157	−0.085
COMT	−0.126	0.07	5.7	2	0.057	0.018	−0.272
DRD4	−0.100	0.196	0.27	2	0.86	0.284	−0.485
	TEMPS-C						
	B	**S.E.**	**Wald**	**df**	***p***	**95%C.I. Lower**	**95%C.I. Upper**
Gender	−0.13	0.066	3.95	1	0.04	−0.001	−0.262
Age	−0.0007	0.005	0.01	1	0.9	0.01	−0.012
BMI	0.008	0.008	1.09	1	0.29	0.296	−0.007
DAT1	−0.045	0.08	0.3	2	0.85	0.12	−0.21
COMT	−0.177	0.111	2.99	2	0.055	0.04	−0.39
DRD4	0.137	0.168	0.83	2	0.65	0.366	0.117
	TEMPS-H						
	B	**S.E.**	**Wald**	**df**	***p***	**95%C.I. Lower**	**95%C.I. Upper**
Gender	−0.07	0.05	2.33	1	0.12	0.021	−0.175
Age	0.0008	0.003	0.05	1	0.81	0.008	−0.006
BMI	0.002	0.006	0.2	1	0.64	0.014	−0.009
DAT1	−0.019	0.06	0.27	2	0.87	0.098	−0.137
COMT	0.12	0.06	6.05	2	0.04	0.241	−0.002
DRD4	−0.07	0.18	2.45	2	0.29	0.282	−0.239
	TEMPS-I						
	B	**S.E.**	**Wald**	**df**	***p***	**95%C.I. Lower**	**95%C.I. Upper**
Gender	0.032	0.094	0.11	1	0.73	0.217	−0.152
Age	0.003	0.008	0.17	1	0.67	0.021	−0.013
BMI	0.005	0.014	0.13	1	0.71	0.033	−0.023
DAT1	0.299	0.143	5.44	2	0.065	0.58	0.019
COMT	−0.35	0.211	5.92	2	0.04	0.074	−0.756
DRD4	0.322	0.207	3.13	2	0.2	−0.084	0.12
	TEMPS-A						
	B	**S.E.**	**Wald**	**df**	***p***	**95%C.I. Lower**	**95%C.I. Upper**
Gender	0.085	0.078	1.18	1	0.27	0.238	−0.068
Age	0.005	0.005	0.8	1	0.37	0.016	−0.005
BMI	−0.008	0.008	0.95	1	0.32	0.008	−0.026
DAT1	−0.08	0.086	1.05	2	0.59	0.349	0.088
COMT	−0.219	0.1	4.2	2	0.12	0.04	−0.009
DRD4	−0.11	0.257	0.21	2	0.89	0.386	−0.623

BMI, body mass index; TEMPS_D—depressive subscale of TEMPS-A; TEMPS_C—cyclothymic subscale of TEMPS-A; TEMPS_H—hyperthymic subscale of TEMPS-A; TEMPS_I—irritable subscale of TEMPS-A; TEMPS_A—anxious subscale of TEMPS-A.

3. Discussion

To date, many studies point to the connection between obesity and mood disorders, such as depression or BD [24–28]. Oniszczenko et al. (2015) suggest that personality traits expressed by temperament may constitute specific risk factors for the development of obesity. Those traits might determine behaviors which hinder weight loss or cause excess eating. Moreover, mentioned temperaments may also contribute to the proneness to mood disorders associated with obesity [29].

Therefore, research on a neurobiological basis of affective temperament could convey essential details of how dopaminergic gene polymorphisms add to the pathogenesis of mood disorders in the obese population; it may, in particular, explain that changes in dopamine transmission may be a causative and a common factor in the development of obesity, as well as of affective diseases [30–32].

In this study, we analyzed affective temperament dimensions in an obese population using the TEMPS-A autoquestionnaire. Subsequently, we scrutinized correlations of affective temperament and dopaminergic gene polymorphisms which are involved in obesity and mood disorders. Those genes are comprised of *COMT* Val158Met, *DAT1* and *DRD4*. To our knowledge, this is the first study analyzing the affective temperament in the context of dopaminergic genes in an obese population.

Tables 1 and 2 show significant differences of affective temperament dimensions in both sexes. According to Table 1, men scored higher than women for the depressed and irritable temperament. The logistic regression model (Table 7) shows significant results for gender and TEMPS-D, but not for the irritable dimension. In our previous study, evaluating the affective temperament in an obese Polish population in the context of the serotonin transporter gene polymorphism (5-HTTLPR), we also observed a higher expression of the irritable temperament in men [23]. Studies show significant differences between temperament dimensions in patients suffering from BDs in comparison to healthy ones. Individuals with BD show greater scores in depressive, cyclothymic, irritable and anxious dimensions [33]. It has been shown that, among bipolar patients, cyclothymic and irritable temperaments may be connected with impulsivity [34]. The French study of Bénard et al. (2017) exhibits a stronger association between impulsivity and obesity in men than in women, suggesting the role of gender in weight status and eating behaviors [35]. Such results are interesting in the context of the proneness to affective disorders in this population, with a differentiation between both sexes.

The literature also shows that females may be more susceptible to depression than men [36]. This may stem from many factors, including sociocultural, psychosocial, or behavioral factors. Considering the molecular basis which connects gender, depression and obesity, the difference in sex hormones may affect a response to stressors and modulate immune responses, resulting in higher inflammation, eventually leading to depressive disorders [37–39]. Sex hormones affect the immune system by exerting pro-, or anti-inflammatory effects. This includes stimulating the immune cell activation, or an increased expression of cytokines which participate in the immune responses. Great evidence points to the link between elevated pro-inflammatory cytokines and depression. The data indicate that the immune system may contribute to depression pathogenesis in different ways due to sex differences. During puberty, a crucial period for depression development, the estradiol levels increase. Also, the interplay between sex hormones and the immune system may be seen in peri- and post-partum depression, where the level of estrogen is also augmented [40]. Androgens take part in the suppression of immune responses, but it has been shown that a greater activation of the immune system in males with a reduced testosterone concentration may contribute to mood disorders [41]. Even though the literature shows mixed results in this field, Byrne et al. (2015) conclude that the female sex may be the factor influencing immune responses and depression [38,42]. More research focusing on differences of affective temperament in both sexes would bring interesting data regarding the genetic and molecular basis of morbidity for mood disorders in men and women.

Affective temperament is considered a stable construct associated with genetic transmission and could serve as a phenotype to detect genes responsible for a susceptibility to affective disorders [18,43,44]. Surprisingly, we have observed the correlations between temperament dimensions and age in both men and women. A positive correlation between a depressive and anxious temperament and age may ensue

from changes of a person's experience during their lifetime. The study of Caserta et al. (2011) showed no connections between depression and the immune system in young girls, although in older girls higher depression measures were associated with increased NK cells cytotoxicity [42]. It has been shown that a positive demeanor, i.e., extraversion, agreeableness, or being optimistic, may affect the immune system, by for example lowering the IL-6 response to the stress factors [45,46]. On the other hand, pessimism contributed to augmented markers of inflammation, like IL-6 and the C reactive protein [47]. We assume, that similar associations might be responsible for our results regarding TEMPS-A, and that sex and age might constitute potential modifiers of affective temperament dimensions. Furthermore, more research should be conducted in relation to the association between anxiety and depressive disorders, in the context of hypothalamic-pituitary-adrenal (HPA) axis dysregulation [48,49].

Epigenetics is a novel field describing alterations in gene functioning without changes within the genome sequence. It provides potential mechanisms explaining the adverse effects of environmental factors on modulatory mechanisms of gene expression, which may exert long-term effects and be putatively heritable [50,51]. Recent studies connect epigenetic changes with numerous diseases including cancer, while laying emphasis on their crucial role in the pathopsychology, by explaining the association between depressive and anxiety disorders, and adverse life events, or the impact of stress in childhood [52–56]. Additionally, in some studies, it has been corroborated that epigenetic changes may exert dysregulations in the HPA axis, by affecting its regulatory genes, thus contributing to stress-related disorders. The upregulation of the cortocotropin-releasing hormone expression or altered transcription of the glucocorticoid receptor in the brain regions may stem from stress-induced epigenetic modifications, and thus be responsible for HPA-axis dysfunction [57,58].

Therefore, we assume that epigenetics might be a putative link connecting received TEMPS-A results and age. Due to the scarce literature regarding this topic, we encourage more research engaged in psychoneuroimmunology or the influence of environmental factors on the affective temperament. Epigenetics constitutes a challenging field which may convey essential data explaining discrepancies in affective temperament investigations.

In the current study, an increased BMI positively correlated with a greater expression of hyperthymic temperament in women and a greater cyclothymic and irritable dimension in men. We can refer to our findings from our previous study. Temperament results between morbid obese (BMI > 40) and obese individuals (BMI ≤ 40) showed that morbidly obese scored greater in hyperthymic and cyclothymic dimensions [23]. In the study of Amann et al. (2009), patients with morbid obesity displayed higher scores in cyclothymic, irritable and anxious dimensions, which is partially consistent with our results [21]. Considering that studies show associations between the cyclothymic, irritable and hyperthymic temperament, and BD, the abovementioned data imply a heightened risk of this disease with a weight gain in obese patients [59–62]. In this study, the cyclothymic temperament in women showed a negative correlation with the BMI and with the age in males, which is inconsistent with findings in the literature [63]. We presume that the heterogeneity of the results may stem from the lack of the control group. It is possible that, when comparing with non-obese individuals, the study group could exhibit a more expressed cyclothymic dimension of the affective temperament.

The association between *COMT* Val158Met and mood disorders has been pointed out in the literature [64–66]. However, many researchers still show some concerns about the exact mechanism by which dopamine transmission, determined by *COMT*, contributes to the origin of affective disorders [67]. Some authors propose that the polymorphisms may influence the HPA axis reactivity and thus, by causing a dysregulation of the inflammation processes, may be involved in the pathogenesis of mood disorders and obesity in a reciprocal manner [68–70]. The literature also shows an association between *COMT* polymorphisms and personality traits in patients suffering from BD [71–73].

Some publications exhibit connections between Met alleles and vulnerability to stress and anxiety, and thus depression [65,74]. However, Massat et al. (2011) showed that the Val allele was more common in individuals with an early stage of depression [75]. The study performed on larger population showed

mixed results: The Met allele occurred less frequently among men with depression in comparison to the control group [76].

During the analysis of the connection between affective temperament and dopaminergic gene polymorphisms, we have only observed the association between *COMT*Val158Met polymorphisms. Considering the affective temperament, *COMT* heterozygotes showed significant results only in irritable and cyclothymic dimensions. Using a logistic regression model (Table 7), we also received significant results concerning the irritable temperament and *COMT* polymorphism. Both temperaments were overrepresented in patients with bipolar disorders [59]. The irritable temperament has been linked with anxiety and agitation and found more often in persons with bipolar disorder, in comparison to healthy controls or patients with a major depressive disorder [62,77].

Previous studies on the COMT relationship with the dimensions of the temperament in Cloninger's concept were focused mainly on the novelty seeking dimension. These studies gave different results, the majority of which focused on the polymorphism rs4680 [78–80]. Golimbet et al. (2007) provided evidence that the *COMT* Met allele (which contributes to the reduction of enzyme activity and ultimately leads to an increase in dopamine levels) was associated with a greater severity of temperamental trait novelty seeking in women [78]. The repetition of this result was done by Tsai and co-workers (2004) on young Chinese women [81]. However, the association of the rs4680 polymorphism of the *COMT* gene with the novelty seeking dimension of temperament has not been confirmed. Searching in other studies conducted on the Caucasian population and the Japanese population [79,80]. In a study conducted on the Chinese population on drug addicts, the *COMT* gene polymorphism was shown to be related to the temperamental characteristics of novelty seeking and the tendency to addiction [82]. A decreased pre-dopaminergic activity and low control, associated with specific *COMT* genotypes, may increase impulsivity, which is a component of novelty seeking. Research by Kang and co-workers (2010) on the dimensions of character showed that the Val158Met *COMT* polymorphism may be related to a susceptibility to boredom and the need for strong sensations in women [83].

The TEMPS-A validation study showed a positive correlation between both the cyclothymic and irritable temperament and the higher novelty seeking scores; hence, our findings are consistent with the results of the abovementioned studies [84], in particular in relation to the fact that Cloninger's novelty seeking, as well as Akiskal's cylothymic and irritable dimension, are involved in affective disorders [85]. In their work, Parneix et al. (2014) found that patients with irritability related to major depressive episodes were characterized with atypical features like weight gain and showed greater novelty seeking. The authors suggested that such findings are indicative of a greater vulnerability to BD [86]. In another study, impulsivity seen in the bipolar spectrum was also described in the context of obesity and food addiction [87]. Thus, the affective temperament seems to be related to a susceptibility to mood disorders in obese individuals, and its evaluation might provide useful information considering treatment approaches.

Unfortunately, due to the observational design of our study and the lack of a control group, it is difficult to explain the molecular basis of the interplay between the dopaminergic transmission modulated by *COMT* and the affective temperament. We speculate that obese individuals, in comparison to healthy persons, show a disturbed dopamine transmission, and that dopaminergic signaling in heterozygotes gives rise to more pronounced affective temperament dimensions. This may constitute the link between *COMT* polymorphisms and affective disorders in the obese population. Moreover, individual changes in the dopaminergic transmission might bias the obtained results and influence the temperament expression or exert differences in one's behavior [88,89]. We propose that future researches of affective temperament should utilize neuroimaging, along with neurogenetic studies, and compare the obtained results with a control group. This measure might elucidate what kind of dopaminergic transmission, determined by *COMT*, is responsible for the pathogenesis of mood disorders in the obese population.

In Tables 4 and 5, we did not observe any statistically significant associations between the affective temperament and polymorphisms of *DAT1* nor *DRD4*.

The literature shows mixed results about the connection between the abovementioned polymorphism and temperament analyzed with various scales. According to Cloninger's theory, the dimension of temperament novelty seeking is, according to this concept, related to the *DRD4* gene. Previous studies on the association of the VNTR polymorphism in the *DRD4* gene suggested association with the dimension of novelty seeking of temperament [90]. However, further studies did not detect a similar relationship, but showed a correlation of the polymorphism (-521 C/T) of the DRD4 gene with impulsivity and novelty seeking. Other researchers have found a connection between the VNTR polymorphism and two mood temperaments: cyclothymic and irritable; however, this study was performed on a healthy volunteer of the Asian population, and therefore it may be difficult to compare the results to our group [87].

Regarding the *DAT1* gene, some studies indicate that the VNTR 3'UTR polymorphism of the *DAT1* gene is associated with novelty seeking; however, other researchers have not obtained similar results [91–93]. The research also indicates the interaction of *DAT1* gene polymorphisms, *DRD4* and neuroticism [94]. The literature shows little findings describing affective temperament measured with TEMPS-Am, and *DRDR4* or *DAT1* polymorphisms, and more studies are needed in this field.

In Table 6, the effect interaction was observed for the anxious dimension and BMI. However, by using a logistic regression we have not obtained significant results for the BMI and any temperament dimension. In the study of Amann et al. (2009), obese patients scored significantly higher in the anxious dimension, as well as for the irritable and cyclothymic factors [21]. Therefore, we assume that persons characterized by an anxious temperament might be at greater risk of further weight gain. Even though we did not find any associations between this dimension and the dopaminergic genes, it could be that an anxious temperament is related to the serotonergic transmission. It could be, in particular, that it has been linked to moderate novelty seeking and greater harm avoidance—which is connected to this type of signaling [95]. Amann et al. (2009) displayed an association between the S allele of the 5HTTLPRI polymorphism in the serotonin transporter gene and greater scores in the following TEMPS dimensions: cyclothymic, irritable and anxious [21]. Gonda et al. (2006) also obtained similar results in the group of women, which indicates the relationship between an affective temperament and the serotonergic transmission [96]. Additionally, in our previous study regarding the *5HTTLPR* polymorphism, subjects homozygous to the S allele exhibited higher scores in anxious and depressive dimensions in comparison to L allele carriers. Such results indicate a stronger connection between the affective temperament measured by TEMPS-A and the serotonergic transmission, instead of dopaminergic signaling in the obese population [23].

In this study we analyzed only one neurotransmitter signaling. We must take into consideration that many factors influence behavior, including other gene polymorphisms or the complex neurotransmitter interactions in different brain areas [96–101]. For instance, functional brain imaging revealed an additive effect of *COMT* Met158 and *5-HTTLPR* S alleles on the response of the amygdale, hippocampal and limbic cortical areas to unpleasant stimuli, suggesting that persons with those alleles may show a lowered resilience against an anxiety mood [101]. An interesting study of Ro et al. (2018) indicates the differences in the expression of glucagon-like peptide 1 and 2 receptors (GLP-!R, GLP-2R) in patients suffering from mood disorders in comparison to healthy controls, with a greater susceptibility connected to higher BMI values. Both GLP-1R and GLP-2R are implicated in neuroprotection and the antidepressant effect [102]. Moreover, it has been found that a lower expression of the leptin receptor in the hippocampus and hypothalamus may have a significant impact on obesity and comorbid depression. Researchers found that obese individuals or those exposed to chronic unpredictable mild stress showed a diminished expression of the leptin receptor [103]. Nonetheless, mood disorders are complex in their nature and constitute a hard challenge for clinicians in their practice. Due to the growing problem of obesity, there is a need for creating more effective preventing programs that tackle the occurrence of affective disorders in this population. Hence, more studies focusing on the molecular basis of the pathogenesis and interplay between both disorders could bring a better understanding, which is essential for predicting the course and nature of the diseases.

4. Materials and Methods

4.1. Participants

The study was conducted on a population of 245 Caucasian people, who were diagnosed with primary obesity. Secondary causes of obesity were excluded in the Clinic of Endocrinology and Diabetology at the Collegium Medicum of the Nicolaus Copernicus in Bydgoszcz on the basis of a subjective and objective medical assessment, as well as on the basis of performed hormonal and metabolic tests. Significant physical diseases, addiction, substance abuse (e.g., cannabis misuse) or psychiatric and neurological illnesses were the excluding factors for participation in the study. All patients, after being given detailed information on the purpose and nature of the study, expressed written and informed consent of their participation. The study obtained the consent of the bioethical commission at the Nicolaus Copernicus University (No 533/ 2008, 15 Dec 2008).

4.2. Clinical Assessments and Measures

Building on the assessed anthropometric factors, the diagnosis of obesity was established. As a factor reflecting the amount of body fat, the BMI index was adopted. It was calculated as the ratio of weight (kg) to square of height (m).

4.3. Psychological Assessment

For the psychological assessment, we utilized the Temperament Evaluation of Memphis, Pisa, Paris and San Diego Autoquestionnaire (TEMPS-A) to perform an analysis of the dimensions of the affective temperament.

4.4. Genotyping

Genomic DNA was obtained from peripheral blood (5 mL) using the method developed by Lahiri and Schnabel (1993) [104]. The blood was collected on the EDTA medium and mixed, before being frozen in liquid nitrogen and stored at −80 °C prior to extraction. The polymorphisms of the *DAT1, COMT* and *DRD4* genes were determined using the polymerase chain reaction (PCR). The following primers were used: *DAT1* forward, 5′-TGTGGTGTAGGGAACGGCCTGAG-3′; *DAT1* reverse, 5′-CTTCCTGGAGGTCACGGCTCAAGG-3′; forward, 5′-AGCTCCAAGCGCGCTCACAG-3′; *COMT* reverse, 5′-CAAAGTGCGCATGCCCTCCC-3′; DRD4 forward: 5′-GCGACTACGTGGTCTACTCG-3′; and *DRD4* rewers: 5′-AGGACCCTCATGGCC TTGC-3′. The PCR products were then separated by agarose gel electrophoresis using O'RangeRuler™ 50 bp DNA Ladder (Fermentas) as a length marker (Figures 1–3).

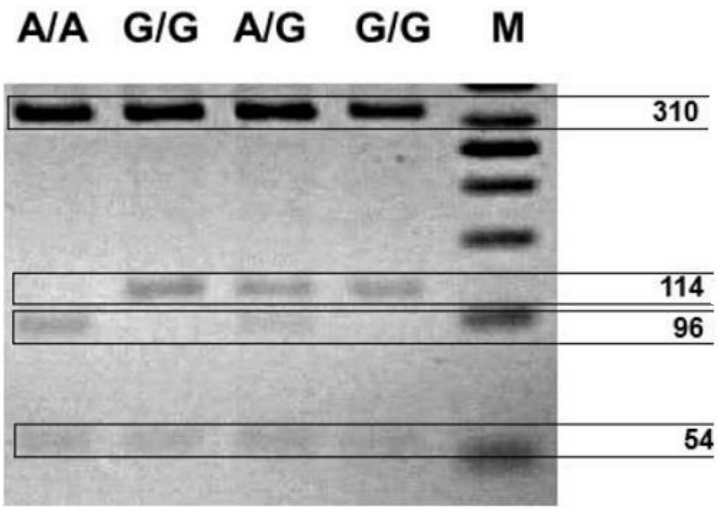

Figure 1. Photo of the digested *COMT* PCR products. The results are labeled by genotype: Met/Met (A/A), 96 bp only; Val/Met (A/G) 114 and 96 bp; and Val/Val (G/G), 114 bp only.

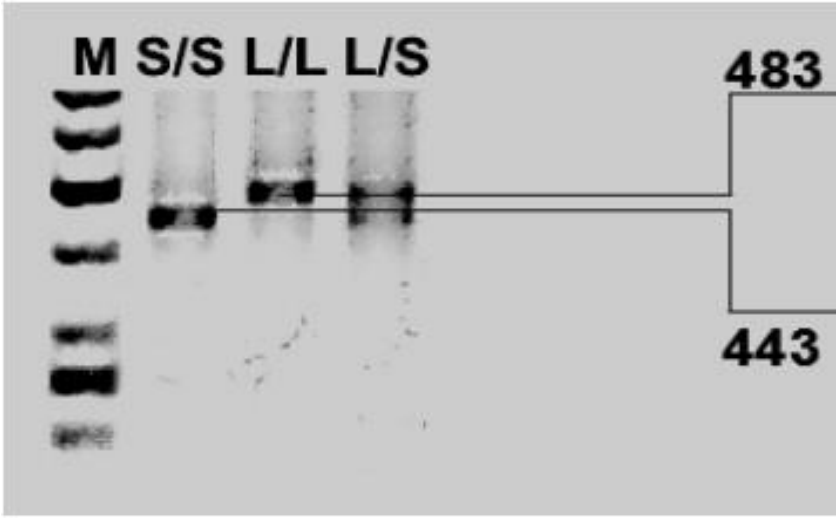

Figure 2. Photo of digested *DAT1* PCR products. The results are labeled by genotype: 10/10 (L/L) 483 bp only; 10/9 (L/S) 483 and 443 bp; and 9/9 (S/S) 443 bp only.

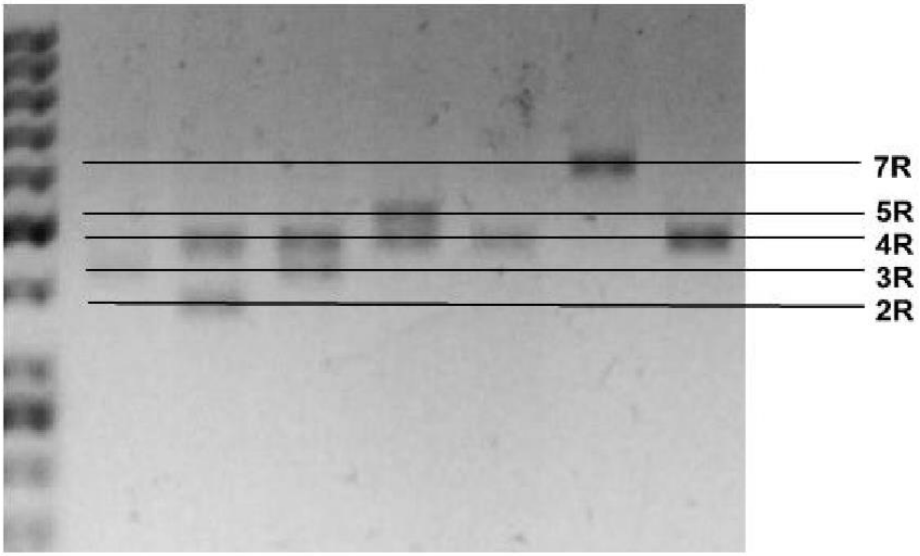

Figure 3. Photo of digested *DRD4* PCR products. Representative photo of separated *DRD4* PCR products depending on the genotype: LL—only 619 bp band (7R); S/S 379 bd (2R) or/and 427 bp (3R) or/and 523 bp (5R) band; L/S – 379 bd (2R) or 427 bp (3R) or 523 bp (5R) and 619 bp (7R) bands.

4.5. Statistical Analysis

Using the Shapiro-Wilk test, it was determined that the test group does not meet the normal distribution criteria. The statistical significance of the differences between the two groups was calculated using the Mann–Whitney U test, and for comparisons with three or more groups, the Kruskal–Wallis analysis of variance (ANOVA) was applied. The NIR Fisher test was used for post hoc analyses. Correlations between two quantitative variables were examined using the Spearman rank correlation test. To control for the effect of age and BMI, which both exhibit significant simple correlations with the dimensions of temperament, we analyzed the data with a partial Kendall regression (partial Kendall's Tau), the nonparametric technique that controls for one confounding [105].

An analysis of covariance (ANCOVA) was performed to examine the interaction effects. An effect size was determined using Cohen's d. The gathered data were analysed by means of StatSoft, Inc. (2017) using Statistica, version 13.0 software and the computer program "Utility Programs for Analysis of Genetic Linkage" (Copyright © 1988 J. Tot) was utilized to test for the goodness of fit to the

Hardy–Weinberg equilibrium. The distributions of all three analyzed genotypes were against the Hardy–Weinberg equilibrium.

Bonferroni corrections were used as multiple testing procedures. A logistic regression of data was performed to predict logit on TEMPS-A temperaments subscales (The Wald statistic in Logistic regression model).

5. Conclusions

To our knowledge, this is the first study analyzing the affective temperament in an obese population in the context of dopaminergic genes polymorphisms, including *COMT* Val158Met, *DRD4*, and *DAT1*. The results of our study indicate the connection between the irritable and cyclothymic dimensions in *COMT* heterozygotes only. We presume that the dopaminergic transmission modulated by these COMT gene polymorphisms may entail a significant expression of cyclothymic and irritable temperaments. This is a very interesting finding, giving rise to more sophisticated research in the future, utilizing neuroimaging studies.

6. Limitations

The main limitation of our study is the lack of a control group in order to gain more reliable results. Second, for the proper evaluation of the connection between the affective temperament and gene polymorphisms, our study group should be larger.

Author Contributions: I state that all authors have made significant contributions in regard to this research. A.B., J.P.-U. and M.B. conceived the idea for the study. J.P.-U. and M.B. contributed to the design of the research. M.B., J.P.-U., N.L. and A.K. were involved in data collection. M.B., N.L., and A.B. were involved in data analyze and interpretation. N.L. and M.B. wrote the manuscript and A.B. with A.T. and R.J. made correction and critically revised the paper. All authors agree to be accountable for all aspects of the work, as well as this manuscript was approved by all authors.

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ORIGINAL RESEARCH

Affective Temperament and Glycemic Control – The Psychological Aspect of Obesity and Diabetes Mellitus

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Purpose: Affective temperament shows innate predisposition to affective disorders and has been studied in patients with type 2 diabetes mellitus (T2DM) and obesity. Studies describing connections between depressive disorders, obesity and T2DM, show a bidirectional way in which these disorders affect each other. Given that obesity, depression, and T2DM are still growing health problems of our times, the improvement of therapeutic strategies is required. The aim of our study was to evaluate affective temperament in obese individuals with T2DM and pre-diabetes and to investigate the correlations between affective temperaments and glycemic control.

Materials and Methods: The study enrolled 185 obese individuals (146 females; 39 males) who were diagnosed with pre-diabetes, diabetes or without any carbohydrate disorder. For affective temperament evaluation, Temperament Evaluation of Memphis, Pisa, Paris and San Diego Autoquestionnaire (TEMPS-A) was utilized; for glycemic control, the assessment of hemoglobin A1c (HbA1c) was performed.

Results: We did not observe any significant differences of affective temperament between studied groups. In the group of patients with diabetes, depressive, cyclothymic and anxious temperaments positively correlated with HbA1c values indicating worse glycemic control. Inversly, hyperthymic dimension showed negative correlation with HbA1c values.

Conclusion: Affective temperaments may affect glycemic control in obese individuals with carbohydrate disorders. Individuals with stronger expression of cyclothymic, depressive and anxious temperaments may need more medical aid for better self-management. Hence, TEMPS-A is an easy and useful tool which may significantly improve the compliance in obese patients with carbohydrate disorders.

Keywords: affective temperament, TEMPS-A, obesity, diabetes mellitus, glycemic control

Introduction

Currently, obesity is perceived as a world crisis. The prevalence of obesity increases every year, hence it creates more challenges for healthcare and economic systems. In 2013, the American Medical Association decided to perceive obesity as a chronic and complex disease to encourage physicians to tackle problems associated with obesity in different ways.[1] It is believed that such aproach will diminish the stigma linked to the development of obesity.

Even though perceiving obesity as a disease still incurs many controversies, this condition is associated with severe complications. Obesity increases risk of disease of almost every system in the body, ie hypertension, dyslipidemia, cardiovascular,

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arthritis, breast cancer, colon cancer or endometrial cancer. In such manner obesity affects mortality and morbidity rates, worsens quality of life, and hinders daily functioning.[2,3]

Type 2 diabetes mellitus (T2DM) is strongly connected with obesity. Its high prevalence in obese people (and the fact that obesity is one of the most important risk factors of T2DM) has led to the term "diabesity". T2DM is a multifactorial disease and is described as a state of hyperglycemia, hyperinsulinemia, and insulin resistance.[4] T2DM contributes to greater rate of cardiovascular disease in adults which is one of the leading causes of death in diabetic patients.[5] In addition, patients with prediabetes, ie, impaired glucose tolerance (IGT) or impaired fasting glucose (IFG) show increased risk of cardiovascular disease, hence greater risk of mortality due to stroke or myocardial infarction.[6]

Literature has shown that both obesity and T2DM exert negative effects on brain functions.[7–9] Those alterations may lead to another fatal disease of our times – depression. Yet, medical databases contain abundant studies proving the link between both T2DM and obesity, and depression. Individuals with T2DM have a greater risk of developing depression compared to healthy controls.[10] There are some researchers who propose a bidirectional relationship between both diseases and common pathways of their pathogenesis.[11,12]

Published meta-analyses yield information about the greater risk of T2DM and metabolic syndrome in patients suffering from mental diseases (bipolar disorder, major depression disorder), hence this group of patients require closer monitoring and screening tests for diabetes.[10,13] Common factors which are involved in the pathogenesis of both mental diseases and metabolic syndrome (which predispose to obesity and T2DM) are: genetic links, endocrine system function, neuroinflammation and epigenetic influence.[14,15] Another meta-analysis confirmed the interplay between obesity and depression; namely depression is a risk factor for obesity, and obesity is a risk factor for depression.[16,17]

Taken together, the interplay between T2DM, obesity, and mental diseases is evident. Therefore, patients with those conditions require a multidisciplinary approach in order to achieve better treatment results, better patient compliance or to diminish the risk of complications related to those disorders.[18] For example, treatment for obesity may improve the course of depression.[19] Cognitive-behavioral therapy implemented in mood disorders may contribute to better patient self-care and ameliorate treatment of diabetes.[20,21]

Building on the connection between the three disorders, it is crucial to develop proper screening tests evaluating predisposition of mental disorders in individuals with obesity or T2DM. In this manner, those patients who are more prone to develop mood disorders might undergo tailored preventive programs or be referred for proper treatment.

Fortunately, there are tests which may be useful in screening for mood diseases. In this study we utilized Temperament Evaluation of Memphis, Pisa, Paris and San Diego Autoquestionnaire (TEMPS-A) - this tool enables assessment of affective temperament which will be described subsequently.

The term affective temperament was proposed by Hagop Akiskal et al. Affective temperament refers to inherited personal traits and may be determined by genetic transmission or biological factors. Throughout life it is a rather stable construct, however its dysregulation can putatively predispose to greater risk of mood disorders.[22–26] Affective temperament consists of five dimensions: cyclothymic, depressive, hyperthymic, anxious and irritable. So far, research results show that utilization of TEMPS-A may provide interesting data regarding the evaluation of patients' predisposition to depression and anxiety or in determining the diagnosis of bipolar disorders.[27,28]

Recent literature shows that TEMPS-A as a tool has been found useful in determining affective disorders and in other conditions like insomnia or pain syndrome.[29–31] The evaluation of affective temperament seems to determine which of the infertile women are more prone to the development of depression and anxiety.[32] Moreover, recent research in a group of gestational diabetes patients showed promising data regarding the association between affective temperament and the development of gestational diabetes, as well as disturbances in glycemic metabolism in this group of patients.[33] Hence, TEMPS-A might be of great utility in determining patients with greater susceptibility of pregnancy complications. Also in our previous work, we found associations between affective temperament dimensions and dopaminergic genes which may be involved in the development of depression in obese patients.[34–36]

Owing to our interesting results concerning affective temperament in obese patients, we decided to take another step in our research. The aim of this study was to scrutinize the relationship between affective temperament and the control of carbohydrate metabolism in obese patients with

diabetes and pre-diabetes. Another main point of our study was to evaluate the differences between the intensity of depressive disorders in those groups of patients, and analyze whether depression is a significant factor associated with glycemic control and affective temperament.

Materials and Methods

Participants

The study enrolled 185 Caucasian people (146 females; 39 males), who were diagnosed with primary obesity. On the basis of a medical history and an oral glucose tolerance test (OGTT) patients were classified into three groups.

The first one - control group - included 87 patients without any carbohydrate disorders (65 women and 22 men), second group of 42 subjects with impaired glucose tolerance (IGT) or impaired fasting glucose (IFG) (33 women and 9 men), and third group of 56 patients (48 women and 8 men) with diabetes. The mean age of participants was 35.8±10.9 (range, 18–68 years) for no carbohydrate disorders group, 43.1±12.5 (range, 18–69 years) for IFG/IGT group, and 51.1±7.1 (range, 31–61 years) for diabetes group. Demographic characteristics are shown in Table 1. Patients were treated at the outpatient clinic at the Endocrinology and Diabetology Clinic and, with the consent of the bioethics committee, were recruited on the basis of a proposal from the attending diabetologist who carried out the therapeutic and diagnostic process. The study was conducted in accordance with the Declaration of Helsinki.

Participants were included in the study according to subsequent criteria: 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. Exclusion criteria included: serious psychiatric or neurological illnesses, addictions to any illicit drugs or alcohol, or any significant somatic diseases.

We provided detailed information about the aims and the nature of the study to participants. We received written informed consent for participation from every patient. In order to conduct the study, we obtained consent of the bioethical commission at the Nicolaus Copernicus University (No 533/ 2008).

Clinical Assessments and Measures

Obesity was diagnosed according to anthropometric measures and the calculation of body mass index (BMI). BMI is a proxy for body fat concentration and is calculated as the ratio of weight (kg) to square of height (m).

Disorders associated with impaired glucose metabolism were diagnosed based on the oral glucose tolerance test performed with 75g of anhydrous glucose in solution. If the patient had a history of diabetes and received adequate treatment, he was included in the diabetic group. Glucose level was obtained at baseline, prior to glucose load, and two hours after glucose intake. Patients fasted for

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 np=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 – 10 (11.5%) II – 23 (26.5%) III – 54 (62%)	I – 5 (12%) II – 12 (28.5%) III – 24.5(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**
BDI	9.0 (6.0–14.0)	7.0 (3.0–15.0)	7.0 (4.0–13.0)	**0.19**	ns.
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**

Notes: Kruskal Wallis ANOVA; Post hoc analysis – Fischer NIR test. Results with statistical significance are presented in bold font.
Abbreviation: BDI, Beck Depression Inventory.

at least 8 hours prior to the OGTT. Depending on the result, the patients were assigned to the study subgroup:

1. if the fasting glucose level was below 99 mg% (5.5 mmol/l) and the level after two hours was below 140 mg% (7.8 mmol/l), the patient had no diagnosis of carbohydrate disorders.
2. If the patient had an elevated fasting glucose level above 100 mg%, and the result after two hours was normal, the patient was diagnosed with abnormal fasting glucose and was included in IFG/IGT group.
3. If the patient had a glucose level after 2 hours in the range of 140 to 199 mg% (7.8–11.1 mmol/l) he was diagnosed with impaired glucose tolerance and was included in the IFG/IGT group.
4. In the case of obtaining a glucose level above 200 mg% (11.1 mmol/l) in the determination after 2 hours, the patient was diagnosed with diabetes.

Metabolic status was analyzed from the blood sample and comprised C-peptide, and for glycemic control hemoglobin A1c (HbA1c).

Psychological Assessment

For psychological assessment, we utilized Temperament Evaluation of Memphis, Pisa, Paris and San Diego Autoquestionnaire (TEMPS-A) to perform an analysis of five affective temperaments.

TEMPS-A measures affective temperaments: depressive, cyclothymic, anxious, irritable and hyperthymic. TEMPS-A questionnaire consists of 110 items for females and 109 for males. Questions regarding each temperament require "yes" (score 1) or "no" (score 0) answers, and are grouped together in the following manner:

1. questions 1 to 21 (21 points) relate to depressive temperament;

2. questions 22 to 42 (21 points) relate to cyclothymic temperament;

3. questions 43 to 63 (21 points) relate to hyperthymic temperament;

4. questions 64 to 84 (21 points, 20 points in the version for men) relate to irritable temperament;

5. questions 85 to 110 (26 points) relate to anxious temperament.

Points scored for each temperament are summed up and then divided by the number of questions pertaining to each dimension. Based on that, the severity of each temperament is measured.[37,38] In our study, the Polish version of TEMPS-A was utilized – TEMPS-A has been validated in a Polish population and showed satisfactory internal consistency.[22,37,38]

To assess the severity of depressive symptoms we used Beck Depression Inventory (BDI). The Beck Depression Inventory was developed by Aaron Beck in 1961.[39] It includes the 21 (A to U) most frequently observed symptoms of depression in the following order: depressed basic mood (sadness), pessimism, feeling inadequate, loss of satisfaction, guilt, expectation of punishment, lack of self-acceptance, self-accusation, wish to die, cry for help, irritability, withdrawal from social contact, lack of decision, distorted body image, difficulties at work, sleep disturbances, fatigue, loss of appetite, weight loss, somatic complaints, low energy levels. The patient is asked to select the severity of the individual symptoms on a scale from 0 to 3. After completing the scale, all points are added up. BDI has been translated into Polish language and validated in a Polish population.[40,41]

Statistical Analysis

Using the Shapiro–Wilk test, it was determined that the test group did not meet the normal distribution criteria. Statistical significance of differences among 3 groups was examined by the Kruskal–Wallis analysis of variance (ANOVA). The NIR Fisher test was used for post hoc analyses. The significance of differences between the two groups was tested using the Mann Whitney U test. Correlation analysis was performed using the R-Spearman correlation test. Analysis of covariance (ANCOVA) was performed to examine interaction among anthropometric (gender, age, BMI), psychological (affective temperaments) effects on fasting glucose and HbA1c. Effect size was determined using Cohen's d. Statistica 13.0 was used for statistical analyses.

Results

Table 1 shows demographic and clinical parameters of the studied groups. The group of patients with diabetes mellitus showed the highest BMI values. Both pre-diabetes and diabetic groups demonstrated significant percentage of comorbid hypertension. However, BDI results were insignificant in all groups.

Typical differences in biochemical parameters related to carbohydrate metabolism were observed in the studied group of patients (Table 2). The group of diabetic patients had the highest levels of not only fasting glucose and

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**

Notes: Kruskal Wallis ANOVA; Post hoc analysis – Fischer NIR test. Results with statistical significance are presented in bold font.

HbA1c, but also C-peptide as a marker of insulin resistance.

Psychometric properties for TEMPS-A, BDI, and biochemicals in study group with a breakdown into women and men are included in Table 3. Men were characterized by a higher level of C-peptide, HbA1c and an irritable temperament.

Further analyses concerned the comparison of the intensity of affective temperaments in the studied subgroups. They did not reveal any significant differences (Table 4).

Table 3 Psychometric Properties for TEMPS-A and BDI in Study Group

	All (n=185)	Women (n=146)	Men (n=39)	P
TEMPS_D	0.42 (0.28–0.52)	0.38 (0.28–0.52)	0.42 (0.23–0.42)	0.09
TEMPS_C	0.38 (0.23–0.57)	0.33 (0.23–0.57)	0.52 (0.23–0.61)	0.12
TEMPS_H	0.52 (0.38–0.61)	0.52 (0.33–0.57)	0.57 (0.38–0.61)	0.37
TEMPS_I	0.19 (0.04–0.28)	0.09 (0.04–0.28)	0.23 (0.09–0.33)	0.01
TEMPS_A	0.32 (0.23–0.52)	0.32 (0.24–0.47)	0.35 (0.17–0.52)	0.34
BDI	9.0 (5.0–18.0)	9.0 (5.0–17.0)	10.0 (5.0–22.0)	0.38
Fasting glucose	95.0 (88.0–111.0)	94.0 (88.0–107.0)	97.0 (90.0–115.5)	0.19
C-peptide	2.99 (2.28–3.9)	2.77 (2.19–3.65)	3.9 (2.7–4.9)	0.003
HbA1c	5.6 (5.3–6.3)	5.6 (5.3–6.1)	5.8 (5.6–6.8)	0.01

Note: Mann–Whitney U test.

Table 4 TEMPS-A Affective Temperament Results in Study Subgroups (Median and Q25-Q75)

	Nondiabetic (n=87)	IFG/IGT (n=42)	Diabetic (n=56)	P
TEMPS_D	0.35 (0.30–0.45)	0.33 (0.27–0.42)	0.42 (0.28–0.47)	0.83
TEMPS_C	0.38 (0.19–0.59)	0.47 (0.23–0.57)	0.47 (0.28–0.57)	0.62
TEMPS_H	0.52 (0.39–0.61)	0.53 (0.38–0.63)	0.57 (0.28–0.61)	0.67
TEMPS_I	0.09 (0.05–0.25)	0.17 (0.04–0.28)	0.19 (0.05–0.33)	0.81
TEMPS_A	0.32 (0.24–0.51)	0.32 (0.23–0.55)	0.35 (0.24–0.47)	0.76

Note: Kruskal Wallis ANOVA; Post hoc analysis – Fischer NIR test.

In subgroups with carbohydrate metabolism disorders - prediabetes and diabetes - the correlations of affective temperaments with the level of fasting glucose and the level of HbA1c were analyzed. In IGT/IFG group, only hyperthymic temperament was significantly associated with higher fasting glucose levels. In the subgroup of diabetic patients, depressive, cyclothymic and anxious temperaments correlated with significantly higher glycemic levels. Inversely, hyperthymic temperament correlated with lower glycemic values. A significantly higher level of HbA1c was associated with a higher intensity of anxious temperament (Table 5).

In the studied group of patients, the ANCOVA analysis of covariance confirmed the significance of the relationship between the cyclothymic temperament and fasting glucose; and anxious temperament and level of HbA1c (Table 6).

Discussion

The aim of this study was to analyze affective temperament in context of biochemical factors in obese patients suffering from diabetes mellitus and pre-diabetes.

Table 5 R-Spearman Correlations of TEMPS-A and BDI Scores with Metabolic Parameters

Results in IGT/IFG Patients				
TEMPS-A	**Fasting Glucose [mg/dl]**	**p**	**HbA1c (%)**	**P**
Depressive	−0.162	0.30	−0.210	0.18
Cyclothymic	−0.049	0.75	−0.079	0.61
Hyperthymic	**0.327**	**0.03**	0.126	0.42
Irritable	0.045	0.77	0.095	0.54
Anxious	−0.096	0.54	0.042	0.79
BDI	0.042	0.79	−0.233	0.13
Results in Diabetic Patients				
TEMPS-A	**Fasting Glucose [mg/dl]**	**p**	**HbA1c (%)**	**P**
Depressive	**0.455**	**0.0004**	−0.226	0.09
Cyclothymic	**0.274**	**0.04**	−0.130	0.33
Hyperthymic	**−0.324**	**0.01**	0.036	0.79
Irritable	−0.119	0.38	−0.257	0.055
Anxious	**0.347**	**0.008**	**0.401**	**0.002**
BDI	0.091	0.50	**0.372**	**0.004**

Note: Results with statistical significance are presented in bold font.

Table 6 ANCOVA Mulitocovariance Test in Diabetes Group

Fasting Glucose		**SS**	**F**	**p**
Gender		1423	3.46	0.09
Age		235	0.57	0.47
BMI		561	1.36	0.27
TEMPS-A	Depressive	899	2.18	0.17
	Cyclothymic	**4407**	**10.7**	**0.011**
	Hyperthymic	1033	2.51	0.15
	Irritable	965	2.35	0.16
	Anxious	1.8	0.004	0.94
HbA1C		**SS**	**F**	**p**
Gender		0.48	1.08	0.32
Age		0.0001	0.0003	0.98
BMI		0.05	0.11	0.74
TEMPS-A	Depressive	0.02	0.05	0.81
	Cyclothymic	0.004	0.009	0.90
	Hyperthymic	0.66	1.48	0.25
	Irritable	0.19	0.44	0.52
	Anxious	**3.41**	**7.58**	**0.02**

Note: Results with statistical significance are presented in bold font.

Results presented in Table 1 indicate that individuals with diabetes mellitus were older and showed greater intensity of obesity in comparison to the other two groups. Those results are consistent with findings of epidemiological studies and publications regarding risk factors of T2DM.[42–44] Also, diabetic patients presented significant results regarding the percentage of hypertension; it is well known that both diseases often appear concomitantly.[45] Comorbidity between hypertension and pre-diabetes was significant as well, which is consistent with findings in the literature.[46]

Obtained scores of BDI in all groups were insignificant. Depression is an important risk factor for both obesity and diabetes. Researchers also established evidence that obesity and diabetes might contribute to greater susceptibility to depression, however there are still many uncertainties regarding the exact mechanism responsible for this pathomechanism.[11,12,16,17] We reckon, that the possible explanation of our results might result from this bidirectional effect between depression, obesity and

diabetes and therefore none of the groups obtained significant results regarding the intensity of depressive symptoms.

Table 2 reflects metabolic results in all three groups of patients. We obtained statistically significant results regarding fasting plasma glucose (FPG) levels, as well as HbA1c values in all groups. Those results are consistent with the definition and diagnostic criteria of IFG and T2DM.[47] Building on these results, the T2DM group showed the worst glycemic control due to elevated HbA1c levels and fasting plasma glucose (FPG).[47–49]

Previously mentioned results also point to the association between obesity and T2DM. The term "diabesity" reflects the close relationship between both obesity and diabetes. Those chronic disorders stem from disturbances involving environmental, genetic, behavioral or physiological factors. Greater calorie intake and lower physical activity, which is characteristic of obesity, may lead to hyperglycemia and insulin-resistance which favor the development of T2DM.[4,50]

Temperament consists of constitutional or genetic aspects of a human's personality. Hagop Akiskal proposed that affective temperament might point to the innate predispositions to affective disorders, if one's exposed to biological or environmental stressors.[23,26]

Obtained results, as shown in Table 4, showed no significant differences of affective temperament dimensions in obese prediabetic and diabetic group. These outcomes point to the environmental relations between diabesity and susceptibility to mood disorders. Genetic factors do not seem to be a common factor connecting vulnerability to affective disorders and obese individuals with T2DM. In their study, Mezuk et al showed strong evidence, that environmental factors rather than genetic ones are involved in the pathomechanisms of T2DM and depressive disorders. One of the most important is stress exposure, which may affect eating habits, leading to overeating foods rich in sugar or fat.[51,52]

Table 5 reflects results of correlations between both: glycemic control (measured with HbA1c) and fasting glucose values; and TEMPS-A dimensions. Obtained data point to the significant relationship between affective temperament and glycemic status in both pre-diabetic and diabetic obese patients.

Diabetes requires proper self-management and, in order to achieve treatment goals, patients need adequate education provided by health professionals.[53] Data show that psychological factors are crucial in glycemic control.[12,54–57] For instance, depression, anxiety or stress may influence daily life choices, the willingness to self-care and adherence to physician's recommendations. It has been shown that psychological support may contribute to better compliance and in this manner enhance therapeutic effects of applied treatment.[53]

The concept that temperament is linked to weight gain has been studied using various questionnaires designed to evaluate temperament, including TEMPS-A.[36,58,59] Evidence has shown that temperament is linked to the progression of metabolic syndrome and central obesity.[60] The study of Altinbas et al even pointed to the relationship between seasons of the year and the greater risk of metabolic syndrome in subjects with depressive temperament.[61] Metabolic syndrome is closely related to obesity and T2DM. Obtained results of obese patients with T2DM point to the positive correlations between FPG levels and temperaments – depressive, anxious and cyclothymic – and HbA1c and anxious temperament. Other researchers have also studied the relation between temperament and glycemic control in diabetic patients and shared similar results regarding the relation between HbA1c and anxious temperament. In their work, Hall et al obtained results showing negative relationship between anxious temperament and HbA1c at the beginning of the diagnosis.[62] Anxious temperament was also a good predictor for pre-diabetes. Taken together, those results display beneficial role of anxious temperament in earlier detection of pre-diabetes and diabetes. Patients with high scores of anxious temperament presented greater motivation for seeking proper medical help, due to their increased concerns regarding their new diagnosis. However, in the group of patients who were already diagnosed with diabetes, anxious temperament was associated with lower physical activity even though this group of patients was already educated about managing their disease. Individuals with anxious temperament, by showing greater concerns and arousal, may hinder proper educational processes which are essential for adequate self-management of diabetes.

Another work of Gois et al obtained results linking depressive and anxious temperament to worse metabolic control expressed with HbA1c values.[63] Both affective temperaments may be viewed as factors predisposing to greater distress which may link the vulnerability to depressive disorders in diabetic patients.[64] The distress may act bidirectionally, ie, emotional distress related to the disease may affect self-care and medication adherence - which may impact HbA1c values; however worse compliance to physician's recommendations and worse glycemic control may bring about greater distress and in this manner influence proper disease management.[65,66] Similar findings

have been obtained in a study which scrutinized the moderating model of affective temperament on the role of depression and diabetes management. Both anxious and depressive temperaments led to greater distress and severity of depressive symptoms which aggravated compliance and glycemic control.[67]

Our results also indicate the positive correlation between cyclothymic and only FPG values. Unfortunately we did not show significant results between cyclothymic temperament and HbA1c. In the work of Yamamoto et al, cyclothymic temperament was significantly associated with worse glycemic control in diabetic patients.[68] The possible explanation is that individuals with cyclothymic temperament seem to be prone to addictive behaviors like overeating and in this manner they try to cope with distress and changes of mood.[69,70] Such behavior may also be responsible for worse compliance in managing T2DM and reflect worse HbA1c values. Published results also indicate that cyclothymic temperament is linked to morbid obesity or eating disorders like binge eating.[59,71,72]

In our study, hyperthymic temperament was associated with higher FPG levels in pre-diabetic patients, but in diabetic ones showed negative correlation with HbA1c values. Established data indicate protective role of hyperthymic temperament in mood disorders, which may be a potential explanation of better coping with distress and better glycemic control.[73] Later in their work, the same authors proposed the dual role of hyperthymic temperament. Within TEMPS-A questionnaire, hyperthymic temperament consists of both protective items like the item concerning self-confidence, as well as risk items which may point to the vulnerability traits similar to irritable temperament – "the irritable components of hyperthymic temperament".[74] Given that irritable temperament has been associated with poor glycemic control in diabetic patients, this may be a possible explanation of ambiguous results of hyperthymic temperament in our study.[75]

To sum up, our results indicate that the evaluation of affective temperament may be useful in the assessment of the course of pre-diabetes and T2DM in obese individuals. Moreover, patients with anxious, depressive and cyclothymic temperament might need even more attention from various specialists (dietitians, psychologists, diabetologists) to adjust proper management of their disease. More research on this issue would provide more interesting and helpful data.

Limitations

The main limitation of this study is the relatively small sample of research groups. Moreover the study lacked a control group of healthy, lean persons.

Conclusion

To our knowledge this is the first study assessing affective temperament glycemic control in obese persons with pre-diabetes and T2DM. Obtained results indicate that cyclothymic, anxious and depressive temperament correlate with worse glycemic control in T2DM, however hyperthymic dimension seems to have a protective effect on glycemia. The evaluation of affective temperament may be useful in order to create more tailored educational programs for obese patients with carbohydrate disorders.

Abbreviations

T2DM, type 2 diabetes mellitus; TEMPS-A, Temperament Evaluation of Memphis, Pisa, Paris and San Diego Autoquestionnaire; TEMPS-A, anxious temperament; TEMPS-D, depressive temperament; TEMPS-I, irritable temperament; TEMPS-C, cyclothymic temperament; TEMPS-H, hyperthymic temperament; HbA1c, hemoglobin A1c; IGT, impaired glucose tolerance; IFG, impaired fasting glucose; FGP, fasting glucose plasma; BDI, Beck Depression Inventory.

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Disclosure

The authors declare no conflicts of interest in association with this manuscript.

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2. WSTĘP

Postęp techniczny w dzisiejszych czasach znacząco wpłynął na życie człowieka. Związany z nim łatwiejszy dostęp do wysokokalorycznego pożywienia przyczynia się do zwiększenia odsetka populacji z nadmierną masą ciała. Postęp istotnie modyfikuje także inne ważne aspekty funkcjonowania człowieka, takie jak ograniczenie aktywności fizycznej oraz tryb życia promując siedzący, które także przyczyniają się do rozwoju nadmiernej masy ciała oraz chorób metabolicznych takich jak cukrzyca.

Według Światowej Organizacji Zdrowia (World Health Organization – WHO) mamy aktualnie do czynienia z kryzysem otyłości. Z każdym rokiem coraz więcej osób ma nadwagę, a także rozwija otyłość – problem dotyczy również dzieci i nastolatków. Dane statystyczne z 2016 r. podają, że na świecie 1,9 miliarda ludzi miała nadwagę, w tym 650 milionów z nich chorowała na otyłość [1].

Otyłość to typowa choroba o złożonym patomechanizmie, w którym rolę mogą brać zarówno czynniki środowiskowe, jak i genetyczne [2]. Ponadto choroba ta związana jest z licznymi powikłaniami dotyczącymi niemal każdego układu w organizmie człowieka jak zespół metaboliczny (w tym dyslipidemie, cukrzyca), nadciśnienie tętnicze, choroby serca, choroby zapalne np. zapalenie stawów oraz choroby nowotworowe, takie jak rak endometrium czy rak jelita grubego. Jedną z głównych chorób związanych z otyłością jest cukrzyca. Szacuje się, że około 20-25% otyłych zachoruje na cukrzycę typu 2 [3]. Dane epidemiologiczne wprost wskazują, że rosnąca liczba pacjentów chorujących na cukrzycę typu 2 związana jest z rozwijającą się pandemią otyłości [4]. W literaturze anglosaskiej coraz częściej używa się terminu "diabesity" (*obesity* – po angielsku otyłość; *diabetes* – cukrzyca), aby podkreślić relację obu chorób w ich wzajemnej patogenezie. Ze względu na liczne powikłania, otyłość istotnie zwiększa ryzyko śmierci i inwalidztwa, a także istotnie obniża jakość życia utrudniając codzienne funkcjonowanie pacjenta [5-8].

Poza chorobami somatycznymi, wiele badań wykazało związek otyłości z dysfunkcją mózgu oraz większą zachorowalnością na choroby psychiczne, takie jak zaburzenia depresyjne czy lękowe [9-12]. Ponadto badania wskazują na dwukierunkową relację w patogenezie obu chorób, tzn. pacjenci z otyłością charakteryzują się wyższym ryzykiem rozwoju zaburzeń depresyjnych, jak i pacjenci z depresją obarczeni są większym ryzykiem rozwoju otyłości [12]. Również cukrzyca typu 2 może doprowadzić do powstania nieprawidłowości w strukturze i funkcjonowaniu mózgu, co przyczynia się do rozwoju depresji. Opublikowane prace sugerują silny związek między depresją i cukrzycą. Wyniki badań wskazują, że czynniki genetyczne, epigenetyczne, hormonalne i immunologiczne mogą odpowiadać za wspólne elementy rozwoju obu chorób [13-15].

Oprócz chorób afektywnych, otyłość przyczynia się do pogorszenia funkcji poznawczych u pacjentów. Prowadzone były i nadal są liczne badania mające odpowiedzieć na pytanie, czy otyłość upośledza funkcje kognitywne w sposób specyficzny, czy też jest to globalne ich pogorszenie. Jednymi z głównych grup funkcji poznawczych są funkcje wykonawcze definiowane jako zestaw wyższych procesów poznawczych, które umożliwiają człowiekowi podejmowanie określonych złożonych działań, umożliwiających osiągnięcie zamierzonego celu [16,17]. Te określone działania związane są z planowaniem, podejmowaniem decyzji, monitorowaniem działań w celu uniknięcia błędu, a także podzielenia czynności na poszczególne etapy i przeprowadzenia ich w odpowiedniej kolejności. Do funkcji wykonawczych należą między innymi kontrola uwagi, kontrola hamowania, hamowanie poznawcze, elastyczność poznawcza oraz pamięć operacyjna [18,19]. Dla przykładu, podczas prowadzenia samochodu kierowca korzysta z funkcji wykonawczych gdy skupia się na tym, co dzieje się na drodze i nie zwraca uwagi na rozmowę swoich pasażerów (czyli hamuje docierające do niego bodźce), ponieważ w przeciwnym wypadku utrudniłyby mu jazdę. W przypadku osób otyłych, które próbują zmienić sposób odżywiania się, to funkcje wykonawcze odpowiedzialne są za powstrzymywanie się od zjedzenia wysokokalorycznego jedzenia silnie pobudzającego układ nagrody [20].

Literatura przedstawia badania naukowe badające funkcje poznawcze u pacjentów otyłych. Wyniki tych prac wykazują, że nadmierna masa ciała związana jest z deterioracją w zakresie uwagi, pamięci, przetwarzania informacji, czy funkcji wykonawczych [21-24]. Jedna z teorii patogenezy otyłości sugeruje, że to zaburzenia funkcji wykonawczych w zakresie kontroli inhibicji doprowadza do rozwoju zaburzeń odżywiania, które powodują nadmiarne łaknienie, a wtórnie wzrost masy ciała [24]. Badania neuroobrazowe również dostarczają dowodów wskazujących na silną korelację między sprawnością funkcji poznawczych a rozwojem otyłości [25]. Tezę, iż to zaburzenia funkcji poznawczych prowadzą do wzrostu masy ciała zdają się potwierdzać badania naukowe, w których wykazano korzystny efekt treningu kognitywnego u osób otyłych w obniżeniu ich masy ciała oraz poprawy stylu życia [26].

Silny związek między depresją a otyłością w kontekście ich patogenezy skłania badaczy do poszukiwania nowych metod diagnostycznych, dzięki którym możliwe będzie wyodrębnienie pacjentów z grupy ryzyka i wdrożenie odpowiedniej profilaktyki zapobiegającej rozwojowi tych chorób.

Już w czasach starożytnych postrzegano temperament jako stały wzór odpowiedzi emocjonalnej [27]. Jeden z czołowych badaczy w dziedzinie psychiatrii, Emil Kraepelin, na tej podstawie stworzył teorię, w której wyodrębnił cztery temperamenty: depresyjny, maniakalny,

cyklotymiczny i drażliwy. Miały one stanowić subkliniczną formę chorób afektywnych [28].

Bazując na pracach Kraepelina, Hagop Akiskal zaproponował termin "temperament afektywny", który odnosi się do wrodzonych cech charakteru, które są uwarunkowane czynnikami genetycznymi lub biologicznymi. Temperament afektywny jest stabilnym, względnie stałym konstruktem, którego zaburzenie może predysponować do rozwoju chorób psychicznych. W związku z założeniem, że temperament afektywny uwarunkowany jest genetycznie, może on służyć jako fenotyp w celu określania genów predysponujących do rozwoju chorób afektywnych [29].

W swoich pracach Akiskal wyodrębnił pięć temperamentów afektywnych: cyklotymiczny, hipertymiczny, depresyjny, lękowy i drażliwy. Osoby z temperamentem depresyjnym są posępne, przygnębione, nieśmiałe i pesymistyczne. Charakteryzują się niską asertywnością, niskim poczuciem własnej wartości oraz negatywnymi przekonaniami na swój temat oraz innych osób i często się obwiniają [30]. W przeciwieństwe do nich, pacjenci z hipertymicznym temperamentem są optymistyczni i towarzyscy. Przejawiają wysoką energię, niską potrzebę snu. Mają wysokie poczucie własnej wartości, są pewni siebie i mają tendencje do obejmowania przywództwa [31]. Pacjenci cyklotymiczni wykazują nagłe zmiany nastroju oscylujące między cechami temperamentu depresyjnego i hipertymicznego [32]. Pacjenci z temperamentem drażliwym mogą przejawiać cechy temperamentu cyklotymicznego, ale prezentują niższy poziom empatii i są bardziej sceptyczni. Takie osoby szybko się irytują, często narzakają i trudno je usatysfakcjonować [31]. Osoby z temperamentem lękowym ciągle odczuwają poczucie zagrożenia, nadmiernie się martwią i mają trudności żeby się uspokoić i rozluźnić [33]. W związku z tym doznają silnego napięcia psychicznego, przekładającego się także na stan somatyczny, co może skutkować prezentowaniem się szeregu objawów.

Badania naukowe dotyczące temperamentu afektywnego wskazują, że jego ocena umożliwia wyszczególnienie pacjentów z wyższym ryzykiem zaburzeń nastroju, takich jak zaburzenia depresyjne czy choroba afektywna dwubiegunowa [32,34]. Interesujące wyniki prezentują badania wykorzystujące ocenę temperamentu afektywnego w chorobach somatycznych np. chorobach autoimmunologicznych, chorobach sercowo-naczyniowych, czy chorobach skórnych [35-39]. Literatura prezentuje również publikacje dotyczące roli temperamentu afektywnego w otyłości, jednak jest ich bardzo niewiele. Praca Amann i wsp. (2009r.) oceniająca temperament afektywny u osób otyłych sugeruje, że otyli różnią się istotnie od osób zdrowych charakteryzując się silniej wyrażonymi temperamentami: cyklotymicznym, drażliwym i lękowym [40]. Wyniki innej pracy na grupie pacjentów z zespołem metabolicznym wskazuje, że za pomocą oceny temperamentu afektywnego możliwa jest ocena czynników genetycznych, które stanowiłyby ryzyko

zachorawania na chorobę afektywną dwubiegunową w tej grupie osób [41]. Inna praca na grupie kobiet z cukrzycą ciążową wykazała, że ocena temperamentu afektywnego mogłaby przynieść korzyści w ewaluacji ryzyka zachorowania na cukrzycę ciążową, a także w kontroli glikemii u ciężarnych z tą chorobą. Wyniki tej publikacji wskazują, że temperament lękowy może stanowić czynnik ryzyka zachorawania na cukrzycę ciążową i z tego względu pacjentki, które silnie prezentują ten wymiar temperamentu wymagają ścisłego monitorowania pod kątem zapadalności na cukrzycę [42].

Związkiem chemicznym mającym kluczowy udział w funkcjach związanych z emocjami, motywacją oraz zachowaniami człowieka, które ukierunkowane są na odczuwanie nagrody jest dopamina [43]. Jest ona głównym neuroprzekaźnikiem w układzie nagrody – skomplikowanej sieci neuronalnej, na którą składają się również szlaki innych neuroprzekaźników. Przekaźnictwo dopaminergiczne w układzie nagrody obejmuje korę czołową i przedczołową, obszary podkorowe oraz jądro półleżące i część brzuszną prążkowia – te dwie ostatnie struktury są kluczowymi obszarami mózgu odpowiedzialnymi za przetwarzanie nagrody, w tym odpowiedzi na naturalne nagrody jakim jest jedzenie z dużą zawartością kalorii. Wykazano, że zaburzenia w szlakach dopaminergicznych układu nagrody mogą być odpowiedzialne za rozwój otyłości i zaburzeń depresyjnych [44-47]. Autorzy formułują teorie patogenezy otyłości wynikające z zaburzeń przekaźnictwa dopaminergicznego: teoria nadmiaru nagrody (*reward surfeit theory*), model wewnętrznej nadwrażliwości (*the incentive sensitization model*) i teoria deficytu nagrody (*reward deficit theory*) [48-50]. Istnieje jeszcze czwarta - związana z zaburzeniami funkcji wykonawczych, która została wcześniej opisana.

Podstawowe czynniki regulujące przekaźnictwo dopaminergiczne są wprost zależne od genów kodujących elementy układu przekaźnictwa dopaminergicznego. W pracy naukowej na bazie której powstała niniejsza analiza doktorska badano wybrane polimorfizmy genetyczne: genu transportera dopaminy typu 1 - *DAT1*, genu receptora dopaminy D4 – *DRD4* i genu katechol-o-metylotransferazy – *COMT* Val158Met (rs4680).

Transporter dopaminy (DAT) odpowiada za regulację stężenia dopaminy w przestrzeni miedzysynaptycznej neuronów dopaminergicznych. DAT głównie skoncentrowany jest w strukturach podkorowych – jądrach podstawy [51]. DAT wychwytuje cząsteczki dopaminy i transportuje je z powrotem do części presynaptycznej. Dzięki temu następuje zmniejszona aktywacja części postsynaptycznej, a tym samym obniża się aktywność dopaminergiczna neuronu. Gen *DAT1* (SLC6A3) znajduje się na chromosomie 5p15.3, zaś polimorfizmy tego genu składają się ze zmiennej liczby tandemowych powtórzeń (VNTR), czyli powtarzających się identycznych

sekwencji par zasad w genomie. Dwa najczęściej występujące allele posiadają dziewięć (A9 lub allel krótki - S) i dziesięć (A10 lub allel długi -L) powtórzeń tandemowych. Badania sugerują, że allel krótki (S) związany jest z większym poziomem dopaminy w prążkowiu. Z kolei allel długi (L) odpowiedzialny jest za wyższe stężenie transportera dopaminy, co prowadzi do zwiększonego zwrotnego wychwytu dopaminy do przestrzeni presynaptycznej, a w związku z tym powoduje zmniejszoną aktywność dopaminergiczną. Niestety opublikowane są również badania, które wskazują na zupełnie odmienną funkcję obu alleli, także dokładny efekt ekspresji poszczególnych polimorfizmów *DAT1* wciąż jest niejasny [52-57].

Enzym COMT jest kolejnym czynnikiem, który moduluje przekaźnictwo dopaminergiczne poprzez katabolizm dopaminy. Działanie enzymu polega na metabolizowaniu dopaminy w przestrzeni międzysynaptycznej. Główna ekspresja enzymu następuje w okolicy kory przedczołowej, ale także w obszarach podkorowych jak prążkowie [58,59]. Gen *COMT* zlokalizowany jest na chromosomie 22q11.2. Najczęstszym polimorfizmem tego genu jest polimorfizm pojedynczego nukleotydu (SNP) - wariant rs4680 (Val158Met), czyli zamiana waliny na metioninę w kodonie 158, przez co dochodzi do translacji enzymu o zmiennej aktywności w zależności of alellów genu [60]. Wykazano, że u osób które są homozygotyczne pod względem allelów metioninowych, enzym COMT ma niższą aktywność i wolniej degraduje dopaminę w przestrzeni międzysynaptycznej, co może skutkować wyższą aktywnością dopaminergiczną w ośrodkach kory przedczołowej. Homozygoty Val/Val posiadają wyższą aktywność enzymu COMT, co może skutkować szybszą degradacją dopaminy prowadzącą do zmniejszonego przekaźnictwa dopaminergicznego [61,62].

Gen *DRD4* koduje receptor dopaminy D4, który zloaklizowany jest w ośrodkach korowych i w mniejszej ilości w ośrodkach podkorowych. Według doniesień, receptor D4 ulega ekspresji głównie w korze przedczołowej, hipokampie i ciele migdałowatym [63,64]. *DRD4* posiada polimofizmy o zmiennej liczbie tandemowych potwórzeń (VNTR). Różne warianty alleli mogą osiągać od dwóch powtórzeń (2R) do jedenastu powtórzeń (11R). Allel *DRD4* 7R koduje receptor dopaminowy o słabszej odpowiedzi receptora w porównaniu do alleli o krótszych łańcuchach zmiennej tandemowej liczby powtórzeń [65,66].

Według teorii opisujących patogenezę otyłości, zaburzenia w przekaźnictwie dopaminergicznym mogą odpowiadać za jej powstawanie. Również w wielu badaniach wykazano, że istnieją odmiany genów modulujących przekaźnictwo dopaminergiczne, które istotnie wiążą się z wyższymi wartościami BMI i dalszym ryzykiem przyrostu masy ciała [67]. Polimorfizm genu *DAT1* A9 związany był z ryzykiem zaburzeń odżywiania, które mogły prowadzić do otyłości [68]. W innym

badaniu wykazano, że osoby homozygotyczne pod względem allelu 9 *DAT1* miały istotnie wyższe BMI [69]. W swojej pracy Yokum i wsp. (2015) badali wpływ polimorfizmów genów dopaminergicznych w otyłości. Wyniki tego badania wskazywały na to, że polimorfizmy genów *DAT1*, *DRD4* i *COMT*Val1158Met, które mogą odpowiadać za większe przekaźnictwo dopaminergiczne, wiązały się ze zwiększoną masą ciała, a tym samym wyższymi wartościami BMI [70].

Badania naukowe w dziedzinie psychiatrii również obejmowały zagadnienie roli przekaźnictwa dopaminergicznego w chorobach afektywnych. Tak zwane *Genome-Wide-Association Study (GWAS)*, czyli badanie asocjacyjne całego genomu wykazały, że polimorfizmy genów zaangażowanych w modulację przekaźnictwa dopaminergicznego są istotnie związane z chorobami psychicznymi. Badania dotyczące polimorfizmów poszczególnych genów również wykazały ich rolę w rozwoju takich chorób jak schizofrenia, choroba afektywna dwubiegunowa czy zaburzenia depresyjne [71-75]. Literatura przedstawia istotny związek allelu Met genu COMT z podatnością na stres oraz lęk, co może stanowić czynnik ryzyka rozwoju zaburzeń depresyjnych lub lękowych [76,77]. Ponadto wykazano związek polimorfizmów COMT z występowaniem zachowań samobójczych u dzieci [78]. Polimorfizm VNTR genu *DAT1* istotnie modyfikował odpowiedź na leczenie lekami antydepresyjnymi u osób chorujących na depresję [79].

Opublikowano również prace badające rolę polimorfizmów genów z poszczególnymi temperamentami afektywnymi w populacji zdrowych osób jak i obciążonych chorobami psychicznymi. Wyniki tych prac wskazują na związek genów przekaźnictwa serotoninergicznego z poszczególnymi wymiarami temperamentu afektywnego [80]. Pacjenci o określonych polimorfizmach genów serotoninergicznych charakteryzowali się temperamentem afektywnym, który mógł predysponować do zaburzeń lękowych [81]. Inne badanie w populacji włoskiej wykazało, że określenie temperamentu afektywnego może istotnie wpływać na relację miedzy polimorfizmami genów przekaźnictwa serotoninergicznego a podejmowaniem próby samobójczej u pacjentów z grupy ryzyka, którzy byli hospitalizowani na oddziale psychiatrycznym [82]. Powyższe przykłady dowodzą, że badania temperamentu afektywnego w kontekście polimorfizmów genów może przyczynić się do lepszego zrozumienia psychopatologii chorób afektywnych. Z uwagi na to, że według badań, przekaźnictwo dopaminergiczne bierze kluczową rolę w rozwoju zaburzeń nastroju, to prace naukowe dotyczące relacji między polimorfizmami genów dopaminy z poszczególnymi wymiarami temperamentu afektywnego, również mogą dostarczyć interesujących danych. Uzyskane informacje mogłyby być następnie wykorzystane w poprawie diagnostyki i leczenia pacjentów z zaburzeniami psychicznymi.

Nawiązując do czwartej teorii patgenezy otyłości związanej z nieprawidłowym działaniem funkcji wykonawczych trzeba podkreślić rolę dopaminy w regulacji poznawczej. W licznych badaniach wykazano, że zaburzenia przekaźnictwa dopaminergicznego są ściśle związane z chorobami, które charakteryzują się deterioracją poznawczą, tj. schizofrenią, zespołem nadpobudliwości psychoruchowej z deficytem uwagi (ADHD) oraz chorobą Parkinsona [83-85]. Jak juz wspomniano, COMT w największym stężeniu zlokalizowany jest w korze przedczołowej, która odpowiada za funkcje wykonawcze. Badania genetyczne wykazały, że osoby z allelem walinowym polimorfizmu *COMT*Val158Met charakteryzowały się gorszymi funkcjami wykonawczymi, w tym pamięcią operacyjną, w porównaniu do osób z allelem metioniny – badano zarówno osoby zdrowe jak i z chorobą afektywną dwubiegunową [86]. Wyniki badań genetycznych potwierdzają prace wykorzystujące neuroobrazowanie – Tan i wsp. uzyskali wyniki wskazujące, że homozygoci COMT Val/Val wykazywali nieefektywną aktywność ośrodków kory przedczołowej podczas wykonywania testów angażujących pamięć operacyjną [87,88]. Istnieją również badania, które przedstawiają zupełnie odmienne wyniki i nie wykazują istotnej roli polimorfizmu *COMT*Val158Met na funkcje wykonawcze [89].

Opublikowano również prace, które przedstawiają związek polimorfizmów pozostałych genów dopaminergicznych z funkcjami wykonawczymi [90,91]. Mimo, że DAT reguluje transmisję dopaminergiczną głównie w strukturach podkorowych jak prążkowiu, to wywiera istotny wpływ na sprawność funkcji poznawczych. W badaniu na zdrowej populacji wykazano, że allele *DAT1* przyczyniające się do silniejszego przekaźnictwa dopaminergicznego w prążkowiu, były również związane z silniejszymi połączeniami z ośrodkami kory przedczołowej, co w efekcie przełożyło się na lepsze wyniki testów oceniających pamieć wykonawczą [92]. Chung i wsp. (2015) w badaniu z wykorzystaniem neuroobrazania uzyskali wyniki wskazujące na to, że homozygoty DAT 10/10 charakteryzowały się niższą objętością istoty białej w obszarach kory przedczołowej co korelowało z większa deterioracją funkcji wykonawczych [93].

Prace naukowe u pacjentów z ADHD wskazują na istotną rolę polimorfizmu *DAT1* na sprawność funkcji wykonawczych, w tym kontroli inhibicji [94,95]. Badanie w grupie osób z ADHD wykazało, że allel 7R genu *DRD4* był odpowiedzialny za deterioracje funkcji wykonawczych [96]. Z kolei osoby z allelem 4R prezentowały sprawniejsze funkcje wykonawcze po przeprowadzeniu tych samych testów neuropsychologicznych [97]. W innych pracach badających rolę *DRD4* na funkcje wykonawcze u pacjentów z ADHD uzyskano niespójne wyniki. W jednym badaniu wykazano, że osoby z allelem 7R prezentowały gorszą kontrolę ihibicji w porównaniu do 4R, zaś drugie badanie, które również dotyczyło pacjentów z ADHD wykazało, że to właśnie osoby z allelem 7R posiadają

lepszą kontrolę inhibicji w przeciwieństwie do homozygot 4R [98,99].

Odmienne wyniki dotyczące roli polimorfizmów genów dopaminergiczych na funkcje wykonawcze może nasuwać wniosek, że istnieją czynniki, które wywierają wpływ na ekspresję tych genów, co następnie prowadzi do zróżnicowanego wpływu produktów tych genów na efektywność funkcji wykonawczych w testach neuropsychologicznych. Jednym z takich czynników może być płeć, a tym samym modyfikujący wpływ hormonów płciowych (estrogeny) na funkcje poznawcze [100-102].

Opisane dotąd wyniki badań, które dotyczyły temperamentu afektywnego, polimorfizmów genów dopaminergicznych oraz funkcji wykonawczych przeprowadzone były na osobach o prawidłowej masie ciała lub czynnik otyłości nie był brany pod uwagę w analizie statystycznej. Literatura przedstawia niewiele prac, które omawiają powyższe zagadnienia w populacji otyłej. Z uwagi na to, że polimorfizmy genów dopaminergicznych, funkcje wykonawcze, a także temperament afektywny wiążą się z patogenezą otyłości, dalsze badania naukowe w tym zakresie przyczyniłyby się do lepszego zrozumienia w jaki sposób osoby zapadają na otyłość. Ponadto wyniki tych badań mogłyby dostarczyć przydatnych informacji w celu lepszego określenia grupy ryzyka pacjentów z otyłością – co wiąże się również z wykreowaniem skuteczniejszych programów profilaktycznych, a także programów leczenia otyłości, zapobiegania jej nawrotom oraz dalszym jej powikłaniom.

Jest to temat szczególnie istotny, ponieważ niestety nawet wśród klinicystów postrzeganie otyłości jako choroby wciąż budzi kontrowersje, a pacjenci otyli są stygmatyzowani przez społeczeństwo, wykluczani, a nawet oskarżani, że otyłość jest efektem ich lenistwa i prowadzenia nieprawidłowego stylu życia. Aby podkreślić rosnący problem otyłości w społeczeństwie, a także chorób z nią związanych, w 2013r. American Medical Association (jedno z wiodących towarzystw medycznych w Stanach Zjednoczonych) ogłosiło, że otyłość to choroba przewlekła o złożonym patomechanizmie i jest związana z licznymi powikłaniami [103-105]. Jest to szczególnie istotne, ponieważ obecne metody zwalczania otyłości nie są wystarczająco skuteczne i choroba często nawraca [106,107]. Dlatego celem tej rozprawy doktorskiej było poruszenie zagadnień związanych z czynnikami poznawczymi, genetycznymi, biochemicznymi a także psychologicznymi otyłości.

3. CELE PRACY

3.1 Problemy badawcze:

1. Czy allele genów modulujących przekaźnictwo dopaminergiczne są związane z nasileniem poszczególnych temperamentów afektywnych u osób otyłych?
2. Czy poszczególne odmiany genów modulujących przekaźnictwo dopaminergiczne są związane z rożnym funkcjonowaniem kory przedczołowej mierzonej za pomocą testu WCST?
3. Czy płeć jest czynnikiem różnicującym wyniki funkcji wykonawczych mierzonych za pomocą testu WCST w grupie otyłych?
4. Czy u osób otyłych z cukrzycą lub stanem przedcukrzycowym, poszczególne wymiary temperamentu afektywnego wykazują istotne zależności z parametrami biochemicznymi wyrównania gospodarki węglowodanowej?

3.2. Hipotezy badawcze:

1. Większe nasilenie otyłości wykazuje dodatni związek z temperamentami afektywnymi związanymi z wyższą podatnością do rozwoju zaburzeń afektywnych oraz współwystępowaniem zaburzeń funkcjonowania kory przedczołowej mózgu.
2. U osób otyłych temperament afektywny związany jest z gorszymi wynikami parametrów biochemicznych wyrównania gospodarki węglowodanowej.
3. Badane polimorfizmy genów przekaźnictwa dopaminergicznego (*COMT*Val158Met, *DAT1, DRD4*) wykazują istotnie różne zależności w aspektach nasilenia otyłości, wyrażenia temperamentów afektywnych oraz funkcjonowania kory przedczołowej mózgu.
4. U osób otyłych płeć jest istotnym czynnikiem różnicującym funkcjonowanie poznawcze zależne od polimorfizmów genów dopaminergicznych (*COMT*Val158Met, *DAT,1 DRD4*).

3.3 Cele szczegółowe:

1. Ocena temperamentu afektywnego za pomocą skali TEMPS-A w populacji otyłych.
2. Ocena nasilenia objawów depresyjnych w grupie badanej.
3. Analiza różnic w zakresie temperamentów afektywnych mierzonych za pomocą kwestionariusza TEMPS-A w polimorfizmach genów dopaminergicznych u osób otyłych.
4. Ocena funkcji wykonawczych w grupie osób otyłych za pomocą testu WCST.
5. Analiza różnic w zakresie parametrów funkcji wykonawczych mierzonych za pomocą WCST w

polimorfizmach genów dopaminergicznych u osób otyłych.

6. Analiza zależności parametrami demograficznymi a wynikami testu WCST.

7. Ocena zależności między wynikami temperamentu afektywnego a zaburzeniami gospodarki węglowodanowej u osób otyłych.

8. Ocena zaburzeń depresyjnych w kontekście wyników skali TEMPS-A, badań biochemicznych gospodarki węglowodanowej oraz czynników demograficznych.

4. METODOLOGIA

Cykl publikacji powstał w oparciu o analizę wyników badania przeprowadzonego na 320 pacjentach - 218 osób stanowiły kobiety, zaś 102 osoby stanowili mężczyźni. Uczestnikami badania były osoby otyłe polskiej narodowości i rasy kaukaskiej w wieku 18-69 lat. Rekrutacja odbywała sie w przyszpitalnej poradni należacej do Kliniki Endokrynologii i Diabetologii w Szpitalu Uniwersyteckim nr 1, im. dr. A. Jurasza.

Po rekrutacji do badania naukowego z każdym pacjentem zebrano wywiad chorobowy, przeprowadzono badanie przedmiotowe, pomiar ciśnienia krwi tętniczej, a także wykonano pomiary antropometryczne. Każdy pacjent był szczegółowo poinformowany o założeniach i celach badania oraz jego przebiegu. Uczestnikom przedstawiono formularz zgody na udział w badaniu, który powstał w oparciu o wzór Komisji Bioetycznej zgodnie z Deklaracją Helsińską. Ponadto Komisja Bioetyczna przy Collegium Medicum wyraziła zgodę na przeprowadzenie badania – nr 533/2008r.

Przyjęto następujące kryteria włączenia do badania:

1. rozpoznana otyłość prosta;
2. pełnoletność;
3. świadoma zgoda na udział w badaniu.

Otyłość prostą rozpoznawano na podstawie obliczonego wskaźnika masy ciała *body mass index* (BMI) wyrażonego w kg/m^2. Wartość równa lub większa od 30 wskazywały na otyłość. Wtórne przyczyny otyłości zostały wykluczone w oparciu o wyniki badań hormonalnych i metabolicznych.

Zastosowano poniższe kryteria wykluczające z badania:

1. obciążenie poważnymi schorzeniami somatycznymi jak np. choroby sercowo-naczyniowe – przy czym obciążenie cukrzycą czy nadciśnieniem tętniczym nie wykluczało z badania;
2. obciążenie chorobami psychiatrycznymi lub neurologicznymi;
3. uzależnienia od substancji psychoaktywnych lub alkoholu;
4. otyłość wtórna.

Osoby włączone do badania miały pobraną krew na badania genetyczne oraz biochemiczne, a także zostały poddane analizie neuropsychologicznej za pomocą testów komputerowych i papierowych kwestionariuszy.

Do poniższych publikacji wykorzystano pogram komputerowy Statistica w wersji 13.0 celem wykonania analizy statystycznej. Na podstawie testu Shapio-Wilka stwierdzono, że dane dla grupy

nie spełniają kryteriów rozkładu normalnego. Różnice istotnie statystycznie między dwiema grupami określono za pomocą testu Mann-Whitney U. Z kolei w celu obliczenia istotności różnic statystycznych między trzema lub więcej grupami wykorzystano analizę wariancji Kurskala-Willisa – test ANOVA. Dla następczych analiz istotności różnic między grupami stosowano analizę post-hoc za pomocą testu NIR Fischera. Do obliczenia istotności poszczególnych zmiennych w zbudowanych modelach stosowano także analizy wieloczynnikowe. Ponadto, wykorzystano test R-Spearmanna w celu obliczenia korelacji między zmiennymi.

Dzięki uzyskanym wynikom badania, po dokonaniu analizy statystycznej, przygotowano trzy publikacje naukowe, które zostały opublikowane w miedzynarodowych czasopismach posiadających współczynnik wpływu – *impact factor* (IF).

Metodologia zastosowana w poszczególnych pracach

4.1. ***Dopaminergic Genes Polymorphisms and Prefrontal Cortex Efficiency Among Obese People – Whether Gender is a Differentiating Factor?*** Current Molecular Medicine (IF-1.600; MNiSW: 70 pkt)

W analizie wykorzystano wyniki 248 otyłych pacjentów (179 kobiet i 69 mężczyzn). Średnia wieku wynosiła 44,5 lat dla kobiet oraz 45 lat dla mężczyzn. Celem analizy była ocena korelacji między funkcą kory przedczołowej a polimorfizmami genów dopaminergicznych *DAT1*, *COMT*Val158Met, *DRD4*.

Do oceny neuropsychologicznej wykorzystano Test Sortowania Kart Wisconsin - *Wisconsin Card Sorting Test* (WCST). WCST umożliwia ocenę funkcji kory przedczołowej w szczególności funkcji wykonawczych, w tym pamięci operacyjnej. W badaniu użyto komputerową wersję testu w języku polskim. Podczas wykonywania WCST osobie badanej na ekranie wyświetlają się w górze ekranu cztery karty wzorcowe. Są to kolejno: karta z jednym czerwonym trójkątem, dwoma zielonymi gwiazdkami, trzema żółtymi krzyżykami i karta z czterema niebieskimi kółkami. Po uruchomieniu testu w dole ekranu wyświetlane są pojedyncze karty (maksymalnie 128), które posiadają symbole i kolory podobne do kart wzorcowych. Celem testu jest dopasowanie wyświetlających się kart do poszczególnych kart wzrocowych zgodnie z regułą: np. karty należy układać według kształtu figur umieszczonych na kartach, ilości tych figur lub koloru tych figur. Osoba badana nie wie, zgodnie z jaką regułą ma dopasowywać karty. Po każdym dopasowaniu karty do talii wzrocowej badany otrzymuje informację zwrotną czy karta została dopasowana w sposób prawidłowy za pomocą napisu w kolorze zielonym "dobrze" lub nieprawidłowy – napis "źle"

w kolorze czerwonym. Dzięki metodzie "prób i błędów", osoba badana musi odkryć zgodnie z jaką regułą należy układać karty do talii wzorcowych. Po pewnym czasie dopasowywania kart, reguła ulega zmianie bez informowania o tym osoby badanej, w związku z czym pacjent musi ponownie odgadnąć nową regułę układania kart. Badanie kończy się gdy zostanie poprawnie ułożonych sześć kategorii lub gdy zostaną wykorzystane wszystkie z 128 kart z talii. Do analizy wyników testu WCST wybrano następujące parametry: 1. odsetek błędów perseweracyjnych (WCST_P), które odzwierciedlają sztywność myślenia oraz trudności w przystosowaniu się do nowych warunków,2. odsetek błędów niepersewerac yjnych (WCST_NP) – jest to liczba błędnych odpowiedzi która świadczy o skuteczności uwagi, 3. liczba poprawnie ułożonych kategorii (WCST_CC), która wiąże się z efektywnością myślenia, a także ukazuje zdolność do prawidłowego reagowania na nowe bodźce. 4. procent odpowiedzi zgodnych z koncepcją logiczną (WCST_CLR) – to parametr, który odzwiercidla zdolność do utrzymania zastosowanej koncepcji logicznej. Ponadto ukazuje zdolność do planowania czynności bazując na otrzymanej informacji. 5. liczba kart potrzebnych do ułożenia pierwszej kategorii (WCST_1st) – pozwala określić doświadczenie w formułowaniu koncepcji logicznej.

Polimorfizmy genów dopaminergicznych, które zostały włączone do analizy, oznaczono za pomocą metod PCR-RFLP i PCR-VNTR. Do genotypowania wykorzystano 10 ml krwi obwodowej od pacjenta. Następnie za pomocą metody Lahiri i Schnabela z krwi obwodowej pozyskano materiał DNA. Na podstawie pozyskanego materiału oznaczono polimorfizmy genów dopaminergicznych: genu transportera dopaminy *(dopamine active transporter – DAT1)*, gen katechologo-O-metylotransferazy *(catechol-O-methyltransferase – COM*Val158Met*)*, gen receptora dopaminergicznego D4 *(dopamine receptor D4 – DRD4)*. Wykorzystano następujące startery genów do reakcji PCR:

1. *DAT1* starter przedni 5'-TGTGGTGTAGGGAACGGCCTGAG-3'; *DAT1* starter wsteczny 5'-CTTCCTGGAGGTCACGGCTCAAGG-3'.
2. *COMT*Val158Met starter przedni 5'-AGCTCCAAGCGCGCTCACAG-3' i *COMT*Val158Met starter wsteczny 5'-CAAAGTGCGCATGCCCTCCC-3'.
3. *DRD4* starter przedni 5'-GCGACTACGTGGTCTACTCG-3' i *DRD4* starter wsteczny 5'-AGGACCCTCATGGCC TTGC-3'.

4.2. ***Association Between Affective Temperament Traits and Dopamine Genes in Obese Population.*** International Journal of Molecular Sciences. 2019;20:1847. (IF: 4,55; MniSW: 140pkt).

W analizie wykorzystano dane 245 pacjentów z otyłością pierwotną – 178 kobiet i 67

mężczyzn. Średnia wieku osób badanych wynosiła kolejno 41 i 42 lata. Celem publikacji była ocena zależności między polimorfizmami genów dopaminergicznych, a wyrażeniem wymiarów temperamentu afektywnego u pacjentów otyłych.

Do oceny psychologicznej wykorzystano polską wersję autokwestionariusza *Temperament Evaluation of Memphis Pisa Paris and San Diego Autoquestionnaire* (TEMPS-A). Kwestionariusz został przetłumaczony na język polski oraz zwalidowany w polskiej populacji [108]. TEMPS-A jest narzędziem opracowanym przez Hagopa Akiskala i za jego pomocą możliwe jest określenie u osoby badanej następujących wymiarów temperamentu afektywnego: cyklotymicznego, hipertymicznego, depresyjnego, drażliwego i lękowego [29]. Skala składa się ze 110 elementów w wersji dla kobiet i 109 elementów w wersji dla mężczyzn. Elementy to zdania twierdzące. Po przeczytaniu danego twierdzenia, badany zaznacza "TAK" jeśli poszczególne twierdzenie jest zgodne z odczuciami osoby badanej, lub "NIE", gdy nie dotyczy osoby badanej. Za każdą odpowiedź "TAK" przyznawany jest 1 punkt, z kolei za odpowiedź "NIE" 0 punktów. W autokwestionariuszu twierdzenia uszeregowane są zgodnie z badaniem konkretnego wymiaru temperamentu w następujący sposób:

1. twierdzenia od 1 do 21 odnoszą się do temperamentu depresyjnego (można uzyskać 21 punktów);
2. twierdzenia od 22 do 42 odnoszą się do temperamentu cyklotymicznego (21 punktów);
3. twierdzenia od 43 do 63 odnoszą się do temperamentu hipertymicznego (21 punktów);
4. twierdzenia od 64 do 84 odnoszą się do temperamentu drażliwego (w wersji dla kobiet 21 punktów, w wersji dla mężczyzn 20 punktów);
5. twierdzenia od 85 do 110 odnoszą się do temperamentu lękowego (26 punktów).

Liczba punktów, która dotyczy poszczególnego wymiaru temperamentu afektywnego jest sumowana, a następnie podzielona przez liczbę twierdzeń przypisaną do tego temperamentu. Na tej podstawie określone jest nasilenie poszczególnych wymiarów temperamentów u osób badanych.

Do artykułu wykorzystano wyniki polimorfizmów genów *DAT1*, *DRD4* i *COMT*Val158Met, których metodę genotypowania opisano wyżej.

4.3. ***Affective temperament and glycemic control – the psychological aspect of obesity and diabetes mellitus.*** Diabetes, Metabolic Syndrome and Obesity: Targets and Therapy. 2021. (IF: 3,168; MniSW: 100pkt).

Celem przygotowania powyższej publikacji wykonano analizę danych dotyczącą roli

temperamentu afektywnego w kontroli glikemii u otyłych pacjentów chorujących na cukrzycę typu 2 lub ze stanem przedcukrzycowym (nieprawidłowa glikemia na czczo i nieprawidłowa tolerancja glukozy). Ponadto oceniono nasilenie objawów depresyjnych i wpływ tych objawów na kontrolę glikemii w tej grupie.

Do analizy wykorzystano dane 185 pacjentów, w tym 146 kobiet i 39 mężczyzn. Pacjentów zestawiono w 3 grupy: pierwszą grupę stanowili otyli bez zaburzeń gospodarki węglowodanowej – 87 osób (65 kobiet i 22 mężczyzn); do drugiej grupy należeli otyli ze stanem przedcukrzycowym – 42 osoby (33 kobiety i 8 mężczyzn); do trzeciej grupy włączono 56 otyłych z cukrzycą (48 kobiet i 8 mężczyzn). Średnia wieku dla wszystkich grup wynosiła kolejno: 35,8 lat (zakres od 18-68 lat) dla grupy pierwszej, 43,1 lat (zakres od 18-69 lat) dla grupy drugiej i 51,1 lat (zakres od 31-61 lat) dla osób z cukrzycą typu 2.

Diagnostyka zaburzeń gospodarki węglowodanowej została przeprowadzona za pomocą testu obciążenia 75g roztworem glukozy – testu OGTT (*Oral Glucose Tolerance Test*). Osoby, które miały już wcześniej rozpoznaną cukrzycę typu 2 i otrzymywały leczenie specjalistyczne, również zostały włączone do badania po okazaniu dokumentacji dotyczącej przebiegu swojej choroby.

Przeprowadzono test OGTT w sposób typowy, tzn. najpierw pobrano krew żylną celem określenia glikemii na czczo (pacjenci nie spożywali posiłków ani płynów przynajmniej na 8 godzin przed testem). Następnie pacjenci spożywali roztwór glukozy i po dwóch godzinach wykonano kolejny pobór krwi w celu oznaczenia glikemii. Na podstawie wyników badania OGTT pacjentów przydzielono do następujących grup:

1. jeżeli poziom glikemii na czczo wynosił mniej niż 88mg% (5,5mmol/l) i po dwóch godzinach glikemia miała wartość niższą niż 140mg% (7,8mmol/l) u pacjenta nie rozpoznawano zaburzeń gospodarki węglowodanowej.
2. jeżeli poziom glikemii na czczo przekraczał 100mg%, a wynik po dwóch godzinach od obciążenia glukozą był prawidłowy, to u pacjenta rozpoznawano nieprawidłową glikemię na czczo i przydzielano osobę badaną do grupy ze stanem przedcukrzycowym.
3. jeżeli poziom glikemii na czczo był prawidłowy, zaś wynik pomiaru uzyskanego po dwóch godzinach od obciążenia glukozą mieścił się w przedziale między 140 a 199mg% (7,8-11,1mmol/l), u pacjenta rozpoznawano nieprawidłową tolerancje glukozy i przydzielano osobę badaną do grupy ze stanem przedcukrzycowym.
4. jeżeli po dwóch godzinach od obciążenia glukozą wynik glikemii przekraczał 200mg% (11,1mmol), u pacjenta rozpoznawano cukrzycę typu 2.

W przeprowadzonej analizie wykorzystano wyniki pomiarów biochemicznych, które

opracowano z próbki krwi żylnej. Były to wyniki hemoglobiny glikowanej A1c (HbA1c), wartość glikemii na czczo – *Fasting plasma glucose* (FPG) oraz wartość C-peptydu. HbA1c oznaczono celem określenia kontroli glikemii przez trzy miesiące, z kolei wyniki C-peptydu świadczyły o nasileniu insulinooporności u pacjentów.

Do analizy psychologicznej wykorzystano autokwestionariusz TEMPS-A, który został opisany powyżej. Do oceny nasilenia objawów depresyjnych wykorzystano Skalę Depresji Becka - *Beck Depression Inventory* (BDI). Skala depresji Becka została opracowany przez Aarona Becka w 1961r i ocenia subiektywne objawy depresji. Skada się z 21 pytań (uszeregowanych od A do U), które dotyczą najcześciej wystąpujących objawów depresji takich jak smutek, poczucie winy, pesymizm, obniżone poczucie własnej wartości, płaczliwość, drażliwość, myśli samobójcze, zaburzony obraz własnego ciała, problemy ze snem, problemy z wykonywaniem pracy, obniżona energia i łatwa męczliwość, a także spadek masy ciała. W każdym pytaniu osoba badana za pomocą odpowiedzi określa nasilenie poszczególnych objawów depresji w skali punktowej od 0 do 3. Po ukończeniu kwestionariusza sumowane są wszystkie punkty. Nasilone objawy depresyjne były rozpoznawane po uzyskaniu więcej niż wartość punktu odcięcia dla polskiej populacji, tzn powyżej 12 punktów. Na cele badania wykorzystano polską adaptacje BDI, która została zwalidowana w polskiej populacji [109,110].

5. CYKL PUBLIKACJI

5.1 Dopaminergic Genes Polymorphisms and Prefrontal Cortex Efficiency Among Obese People – Whether Gender is a Differentiating Factor?

Pierwsza z publikacji włączonch do rozprawy doktorskiej została opublikowana w czasopiśmie Current Molecular Medicine. Przeprowadzona analiza dotyczyła oceny funkcji wykonawczych wyrażonych za pomocą testu WCST i ich korelacji z polimorfizmami genów dopaminergicznych – *COMT*Val158Met, *DAT1* i *DRD4* w populacji otyłej. Ponadto celem analizy była również ocena roli płci w deterioracji poznawczej również w kontekście polimorfizmów genów dopaminergicznych.

Wyniki korelacji między parametrami takimi jak: wiek, BMI oraz wyniki testu WCST a płcią męską i żeńską wykazały, że zarówno u kobiet jak i u mężczyzn wiek związany był z gorszymi wynikami testu WCST (Tabela 1). Jedynie w grupie kobiet wykazano istotną korelację między wzrostem BMI a podwyższoną liczbą błędów perseweracyjnych i niepersewerac yjnych, a także z niższą ilością odpowiedzi zgodnych z koncepcją logiczną (WCST_CRL). Pozytywna korelacja między BMI a błędami perseweracyjnymi może świadczyć o zaburzeniach kontroli inhibicji. Zaburzenia tego rodzaju mogą przełożyć się na dalszy wzrost BMI i są zgodne z teorią patogenezy otyłości dotyczącą deterioracji funkcji wykonawczych.

Ocena korelacji polimorfizmów genu *COMT* w grupie kobiet wykazała, że osoby z polimorfizmem Met/Met lub Met/Val charakteryzowały się lepszymi wynikami testu WCST w porównaniu do homozygot Val/Val, jednak po przeprowadzeniu analizy wieloczynnikowej otrzymane wyniki znalazły się na granicy istotności statystycznej (Tabela 2). Prace dotyczące oceny związku genu COMT z funkcją kory przedczołowej wskazują, że lepsze działanie funkcji poznawczych może być związane z bardziej nasilonym przekaźnictwem dopaminergicznym uwarunkowanym allelem Met, w porównaniu do allelu walinowego [111-114]. Według Tabeli 2 w grupie kobiet lepsze wyniki testu WCST uzyskane przez heterozygoty mogą wskazywać na zależność o charakterze odwróconej litery U między nasileniem przekaźnictwa dopaminergicznego, a sprawnością funkcji wykonawczych. Jeżeli przekaźnictwo dopaminergiczne jest zbyt nasilone lub za słabe, może to skutkować deterioracją funkcji wykonawczych.

Analiza grupy kobiet i mężczyzn w kontekście polimorfizmu genu *DAT1* ujawniła, że w grupie kobiet w wieku powyżej 45 roku życia, allel 10 (długi) związany był z lepszymi wynikami testu WCST. Z kolei w grupie kobiet poniżej 45 roku życia nie zaobserwowano żadnych korelacji z

parametrami WCST. W grupie mężczyzn powyżej 45 roku życia zaobserwowano istotnie więcej błędów niepersewerac yjnych u homozgyt 10/10. Podobnych wyników nie uzyskano w grupie kobiet (Tabela 3 i 4). W piśmiennictwe dostępne są badania, które również wskazują na powiązanie allelu 10R z gorszymi parametrami poznawczymi [115,116]. Różnice w uzyskanych wynikach testu WCST między otyłymi kobietami, a mężczyznami w kontekście polimorfizmów genu *DAT1* mogą wynikać z wpływu estrogenów na transmisję dopaminergiczną. Dane pozyskane z piśmiennictwa wskazują na odwracanie działania DAT i zwiększenie napływu dopaminy do przestrzeni międzysynaptycznej przez estradiol, co może skutkować nasileniem przekaźnictwa dopaminergicznego w obszarach podkorowych [117].

Analiza wyników korelacji między wynikami testu WCST a polimorfizmami genu *DRD4* w grupie kobiet i mężczyzn wykazała, że w grupie kobiet powyżej 45 roku życia allel L (długi) korelował z lepszymi wynikami w zakresie WCST_1st (Tabela 5 i 6). Nasilenie przekaźnictwa dopaminergicznego, które może być uwarunkowane przez ten polimorfizm prawdopdobnie przyczynia się do lepszego działania kory przedczołowej w zakresie funkcji wykonawczych. Inne prace badające rolę polimorfizmów genu *DRD4* na funkcje wykonawcze wykazały, że nasielenie przekaźnictwa dopaminergicznego wpływa na funkcje wykonawcze w postaci odwróconej litery U [118]. Oznacza to, że miernie nasilone przekaźnictwo dopaminergicze uwarunkowane polimorfizmami genu *DRD4* przyczynia się do sprawniejszego działania funkcji wykonawczych.

Uzyskane wyniki analizy potwierdziły hipotezy badawcze nr 1, 3 i 4.

5.2 Association Between Affective Temperament Traits and Dopamine Genes in Obese Population.

Publikacja ukazała się w 2019r. w czasopiśmie International Journal of Molecular Sciences. Praca dotyczy analizy korelacji między wymiarami temperamentu afektywnego a polimorfizmami genów dopaminergicznych, które powiązane są z patogenezą otyłości oraz występowaniem zaburzeń depresyjnych w grupie osób otyłych. Do tej pory nie ukazał się artykuł opisujący powyższe zagadnienie.

Celami pracy było określenie, czy istnieje korelacja między wzrostem BMI, a wymiarami temperamentów afektywnych, które wiążą się z większym ryzykiem rozwoju zaburzeń depresyjnych. Kolejnym etapem analizy była ocena, czy również polimorfizmy genów dopaminergicznych korelują wymiarami temperamentu afektywnego, które predysponują do rozwinięcia się zaburzeń depresyjnych.

W grupie kobiet uzyskano pozytywną korelację między wartościami BMI, a temperamentem

hipertymicznym. Z kolei u mężczyzn BMI pozytywnie korelowało z wymiarami temperamentu cyklotymicznym i drażliwym (Tabela 7). Otrzymane wyniki częściowo pokrywają się z danymi z piśmiennictwa. W badaniu oceniającym temperament afektywny w grupie otyłych wyniki wskazywały, że otyłość olbrzymia związana była z silniejszym wyrażeniem temperamentu hipertymicznego [119]. Wyniki innej pracy na grupie otyłych wykazały, że pacjenci z otyłością olbrzymią charakteryzowali się wysoką punktacją w zakresie temperamentów cyklotymicznego, drażliwego i lękowego [40]. Tym samym potwierdzono hipotezę nr 1.

Analiza polimorfizmów genów dopaminergicznych *COMT*Val158Met, *DAT1* i *DRD4* oraz wymiarów temperamentu afektywnego, ujawniła istotne korelacje jedynie w przypadku polimorfizmów genu *COMT*. Grupa heterozygot genu *COMT* istotnie korelowała z nasileniem cyklotymicznego i drażliwego temperamentu w kwestionariuszu TEMPS-A (Tabela 8). Według literatury zarówno temperament drażliwy jak i cyklotymiczny są silniej wyrażone w grupie osób z chorobą afektywną dwubiegunową [120]. Uzyskane wyniki badań mogą świadczyć o roli temperamentu afektywnego i przekaźnictwa dopaminergicznego uwarunkowanego polimorfizmem genu *COMT* w patogenezie zaburzeń nastroju w populacji otyłej.

W przeprowadzonej analizie nie wykazano istotnych korelacji temperamentu afektywnego z polimorfizmami genów *DAT1* i *DRD4* (Tabela 9 i 10). W dostępnej literaturze znajduje się mało doniesień dotyczących związku między temperamentem afektywnym i polimorfizmami tych genów.

Na podstawie przeprowadzonej analizy częściowo potwierdzono hipotezę nr 3.

5.3 Affective temperament and glycemic control – the psychological aspect of obesity and diabetes mellitus.

Ostatnia publikacja włączona do cyklu została opublikowana w 2021r. w czasopiśmie Diabetes, Metabolic Syndrome and Obesity: Targets and Therapy. Celem analizy była ocena temperamentów afektywnych w kontekście czynników biochemicznych u pacjentów otyłych chorujących na cukrzycę typu 2 lub ze stanem przedcukrzycowym.

W pierwszej analizie nie stwierdzono istotnych różnic w nasileniu temperamentów afektywnych między grupami otyłych, pacjentów ze stanem przecukrzycowym oraz pacjentów bez zaburzeń gospodarki węglowodanowej (Tabela 11). Otrzymane wyniki wskazują, że prawdopodobnie nie ma czynnika genetycznego, który byłby odpowiedzialny za ryzyko zaburzeń nastroju u otyłych pacjentów z zaburzeniami gospodarki węglowodanowej w porównaniu do pacjentów wyłącznie otyłych. Prawdopodobnie czynniki zewnętrzne, jak np. odczuwany stres, mogą przyczynić się do patogenezy zaburzeń afektywnych w tej grupie pacjentów [121,122].

Kolejnym etapem analizy była ocena korelacji między czynnikami biochemicznymi, tj. Wartościami HbA1c (parametr określający kontrolę glikemii) i glikemią na czczo (FPG). Zarówno u osób z cukrzycą typu 2 jak i stanem przedcukrzycowym wykazano istotności w zakresie nasilenia wymiarów temperamentu afektywnego. U otyłych z cukrzycą typu 2 uzyskano pozytywne korelacje między wartością FPG a następującymi wymiarami temperamentu afektywnego: depresyjny, cyklotymiczny, lękowy. Z kolei temperament hipertymiczny ujemnie korelował z wartościami FPG. Stwierdzono również pozytywną kolerację HbA1c z nasileniem temperamentu lękowego. W przypadku otyłych ze stanem przedcukrzycowym uzyskano pozytywną korelację temperamentu hipertymicznego i wartości FPG (Tabela 12). Uzyskane wyniki wskazują na związek między nasileniem temperamentu afektywnego, a wartościami glikemii u pacjentów otyłych z zaburzeniami gospodarki węglowodanowej. Pozytywna korelacja między HbA1c a temperamentem lękowym zdaje się świadczyć o gorszej kontroli glikemii u tych pacjentów, u których ten temperament jest silnie wyrażony. W opublikowanych do tej pory pracach wykazano istotną rolę czynników psychologicznych w kontroli glikemii. Ponadto wdrożenie terapii behawioralnej u pacjentów z czynnikami ryzyka doprowadziło do poprawy stosowania się pacjentów do zaleceń diabetologa, a tym samym uzyskania pozytywnego efektu terapeutycznego w leczeniu cukrzycy [123-125].

Analiza korelacji między temperamentami afektywnymi a czynnikami biochemicznymi w grupie pacjentów ze stanem przedcukrzycowym oraz pacjentów z cukrzycą typu 2 wykazała, że u pacjentów ze stanem przedcukrzycowym temperament hipertymiczny pozytywnie korelował z wartościami FPG. W grupie pacjentów z cukrzycą typu 2 uzyskano wyniki świadczące o negatywnej korelacji z FPG (Tabela 12). Dane z piśmiennictwa świadczą o ochronnej roli temperamentu hipertymicznego w patogenezie chorób afektywnych [126]. Pacjenci, którzy uzyskali wysoką punktację w zakresie temperamentu hipertymicznego w TEMPS-A zdają się lepiej radzić z sytuacjami stresowymi, a w związku z tym, mogą mieć mniej trudności w stosowaniu się do zaleceń lekarskich i kontrolowaniu glikemii. Wyniki z przeprowadzonej analizy wskazują, że temperament hipertymiczny korelował z niższymi wynikami FPG u osób z cukrzycą typu 2, a tym samym lepszym statusem glikemii. Pacjenci ze stanem przedcukrzycowym otrzymali odmienne wyniki dotyczące korelacji między temperamentem hipertymicznym a FPG. Dane z piśmiennictwa wskazują na dwa elementy z których składa się temperament hipertymiczny. Jednym z nich jest element ochronny, który ujawnia się poprzez wysokie poczucie własnej wartości czy pewność siebie. Drugi element zawiera cechy temperamentu drażliwego. Wyniki badań wskazują na to, że pacjenci z silnie wyrażonym temperamentem drażliwym mieli trudności z odpowiednim stosowaniem się do

zaleceń, a tym samym z kontrolą glikemii [127,128]. Powyższe wyjaśnienie może tłumaczyć negatywną koleracją między temperamentem hipertymicznym, a wartościami FPG w grupie pacjentów ze stanem przedcukrzycowym.

Przeprowadzona analiza tym samym potwierdza hipotezę nr 2.

6. PODSUMOWANIE I PRAKTYCZNE IMPLIKACJE WYKONANYCH BADAŃ

Otyłość to choroba przewlekła i złożona, która związana jest z licznymi powikłaniami. Spośród nich istotne są zaburzenia depresyjne oraz zaburzenia metaboliczne, jak cukrzyca typu 2. Ze względu na to, że z każdym rokiem rośnie liczba pacjentów chorujących na otyłość, a także tych u których rozwijają się zaburzenia depresyjne i zaburzenia gospodarki węglowodanowej, kluczowym jest wytworzenie odpowiednich programów profilaktycznych, a także metod diagnostycznych i leczniczych.

W przeprowadzonym cyklu publikacji dokonano analizy polimorfizmów genów dopaminergicznych, także badania funkcji poznawczych i temperamentu afektywnego w populacji otyłej. Ponadto oceniono korelację temperamentu afektywnego z czynnikami biochemicznymi w populacji otyłej obciążonej zaburzeniami gospodarki węglowodanowej.

W pierwszej z przeprowadzonych analiz wykazano, że w grupie otyłych funkcje wykonawcze zależne są od nasilenia transmisji dopaminergicznej w kształcie odwróconej literu "U", co jest uwarunkowane przez polimorfizm genu *COMT*Val158Met. Różnice w wynikach testu oceniającego funkcje wykonawcze między otyłymi kobietami, a mężczyznami może wynikać z hormonów płciowych, tj. estrogenów, które wpływają na transmisję dopaminergiczną.

W drugiej pracy analizowano korelację temperamentu afektywnego z polimorfizmami genów dopaminergicznych. Otrzymane wyniki wskazują na to, że istnieje zależność między polimorfizmem genu *COMT* a nasileniem wymiarów temperamentu afektywnego: drażliwego i cyklotymicznego. Przekaźnictwo dopaminergiczne uwarunkowane przez polimorfizm tego genu może przyczynić się do ekspresji cech temperamentów drażliwego i cyklotymicznego. Cechy te mogą stanowić czynnik ryzyka rozwoju chorób afektywnych w grupie pacjentów otyłych. Na podstawie analizy polimorfizmy genów *DRD4* i *DAT1* zdają się nie wpływać na nasilenie poszczególnych wymiarów temperamentu afektywnego.

Ostatnia praca z cyklu publikacji dotyczyła oceny roli temperamentu afektywnego ze statusem glikemii oraz kontrolą glikemii u pacjentów otyłych z zaburzeniami gospodarki węglowodanowej. Wyniki analizy nie wykazały, różnicy w kontekście wymiarów temperamentu

afektywnego u pacjentów otyłych z cukrzycą typu 2 lub stanem przedcukrzycowym w porównaniu do pacjentów otyłych. Tym samym, pacjenci otyli z zaburzeniami gospodarki węglowodanowej prawdpodobnie nie posiadają dodatkowego (genetycznego) czynnika ryzyka, który by sprzyjał rozwojowi chorób afektywnych. Przeprowadzona analiza wykazała związek mięzy wymiarami temperamentu i statusem glikemii zarówno u pacjentów obciążonych cukrzycą typu 2 jak i stanem przedcukrzycowym. W grupie otyłych z cukrzycą typu 2 temperament lękowy może przyczynić się do gorszej kontrolii glikemii wyrażonej za pomocą HbA1c. Ponadto uzyskane wyniki badań wskazują na dwuznaczną rolę temperamentu hipertymicznego w statusie glikemii u pacjentów ze stanem przedcukrzycowym i cukrzycą typu 2.

Wyniki badań, które uzyskano w cyklu publikacji mogą przyczynić się do usprawnienia programów profilaktyki zaburzeń depresyjnych u pacjentów otyłych. Ocena temperamentu afektywnego jest prostym i krótkim badaniem, które umożliwia wstępną ocenę ryzyka rozwoju chorób afektywnych. Dzięki temu możliwe byłoby szybsze objęcie opieką psychologiczną lub psychiatryczną pacjentów otyłych, co mogłoby zapobiec dalszemu rozwojowi powikłań związanych z chorobami psychicznymi.

Ocena temperamentu afektywnego, może być także korzystna do wyodrębnienia grupy pacjentów otyłych z zaburzeniami gospodarki węglowodanowej, którzy ze względu na aspekty psychologiczne prezentują gorszą kontrolę glikemii. Uzyskane wyniki badań w tym zakresie, mogą przyczynić się do rozwoju nowczesnych terapii behawioralnych, które zapewniłyby pacjentom odpowiednią edukację, a tym samym poprawiłyby stosowanie się pacjentów do zaleceń diabetologicznych.

Ponadto ocena polimorfizmów genów dopaminergicznych wskazuje na istotną rolę czynników genetycznych w rozwoju zaburzeń funkcji poznawczych u pacjentów otyłych, które mogą między innymi przyczynić się do dalszego wzrostu masy ciała. Kolejnym istotnym aspektem jest rola różnic płci w funkcjonowaniu kory przedczołowej. Uzyskane wyniki przyczyniają się do lepszego poznania roli dopaminy w rozwoju deterioracji poznawczej w grupie otyłych pacjentów i wyznaczają tor dalszych badań w tym zakresie.

7. ZAŁĄCZNIKI

Tabela 1. Korelacja R-Spearman'a w grupie kobiet i mężczyzn między wiekiem, BMI a wynikami testu WCST.

	Kobiety (n = 179)		Mężczyźni (n = 69)	
	Wiek	BMI	Wiek	BMI
WCST_P	r= 0.20; p=0.006	r= 0.16; p=0.02	r= 0.37; p=0.001	r= -0.12; p=0.62
WCST_NP	r= 0.27; p<0.001	r= 0.19; p=0.01	r= 0.46; p<0.001	r= 0.001; p=0.99
WCST_CLR	r= -0.24; p=0.001	r= -0.15; p=0.04	r= -0.56; p<0.001	r= 0.06; p=0.62
WCST_CC	r= -0.21; p=0.01	r= -0.04; p=0.59	r= -0.45; p<0.001	r= 0.11; p=0.36
WCST_1st	r= 0.21; p=0.02	r= 0.11; p=0.14	r= 0.27; p=0.02	r= -0.21; p=0.08

BMI, body mass index; WCST_P – odsetek błędów perseweracyjnych (%); WCST_NP – odsetek błędów niepersewerac yjnych (%); WCST_CLR – procent odpowiedzi zgodnych z koncepcją logiczną(%); WCST_CC – odsetek poprawnie ułożonych kategorii(%); WCST_1^{st} – liczba kart potrzebnych do ułożenia pierwszej kategorii.

Tabela 2. Analiza polimorfizmów COMT i wyników WCST w grupie kobiet i mężczyzn.

	Kobiety (n = 179)				Mężczyźni (n = 69)			
	G/G (n= 59)	G/A (n= 74)	A/A (n= 46)	P	G/G (n=12)	G/A (n=44)	A/A (n=13)	P
BMI	42.1 (38.4 – 45.5)	41.5 (36.4 – 47.5)	42.9 (37.2 – 47.9)	0.80	36.1 (31.4 – 40.5)	44.0 (39.4 – 51.2)	38.8 (30.5 – 48.3)	0.04 Post hoc G/G vs AA 0.02
WCST_P	13.5 (9.0 – 16.0)	11,0 (7.0 – 13.0)	12.0 (8.0 – 20.0)	0.05 Post hoc G/G vs A/A 0.02	9.0 (7.0 – 37.0)	9.0 (6.0 – 12.0)	9.0 (7.0 – 20.0)	0.62
WCST_NP	12.0 (8.0 – 20.5)	10.0 (7.0 – 13.0)	10.0 (8.0 – 17.0)	0.23	13.5 (8.0 – 19.0)	11.0 (5.0 – 21.0)	8.0 (6.0 – 17.0)	0,86
WCST_CLR	64.0 (42.0 – 80.5)	75.0 (66.0 – 82.0)	72.0 (49.0 – 79.0)	0.08	72.0 (27.0 – 81.0)	73.0 (58.0 – 83.0)	81.0 (33.0 – 84.0)	0,64
WCST_CC	6.0 (4.0 – 6.0)	6.0 (6.0 – 6.0)	6.0 (3.0 – 6.0)	0.05 Post hoc G/G vs AA 0.03 G/A vs AA 0.02	6.0 (0.0 – 6.0)	6.0 (3.0 – 6.0)	6.0 (5.0 – 6.0)	0,79
WCST_1st	13.0 (11.0 – 24.5)	12.0 (11.0 – 12.0)	12.0 (11.0 – 25.0)	0.03 Post hoc G/G vs AA 0.04 G/A vs AA 0.04	22.0 (12.0 – 129.0)	12.0 (11.0 – 23.0)	12.0 (11.0 – 18.0)	0,27

BMI, body mass index; WCST_P – odsetek błędów perseweracyjnych (%); WCST_NP – odsetek błędów niepersewerac yjnych (%); WCST_CLR – procent odpowiedzi zgodnych z koncepcją logiczną(%); WCST_CC – odsetek poprawnie ułożonych kategorii(%); WCST_1st – liczba kart potrzebnych do ułożenia pierwszej kategorii. Istotne różnice między podgrupami określono za pomocą testu Kruskal-Wallis ANOVA. Analiza post hoc została przeprowadzona za pomocą testu NIR Fishera.

Tabela 3. Analiza polimorfizmów DAT i wyników WCST w grupie kobiet w wieku ≤ 45 r.ż. i > 45 r.ż.

	Kobiety ≤45 (n = 99)				Kobiety >45 (n = 80)			
	L/L (n= 47)	L/S (n= 41)	S/S (n= 11)	P	L/L (n=41)	L/S (n=31)	S/S (n=8)	P
BMI	40.9 (37.2 – 44.8)	42.7 (36.2 – 48.8)	40.1 (37.2 – 41.9)	0.54	43,5 (34.1 – 52.4)	40.8 (35.5 – 47.4)	48.8 (40.2 – 57.0)	0.63
WCST_P	9.0 (7.0 – 13.0)	10.0 (7.0 – 15.0)	10.5 (9.0 – 12.0)	0.80	11.0 (7.0 – 13.0)	13.5 (9.5 – 19.0)	12.0 (8.0 – 22.0)	0.24
WCST_NP	9.0 (7.0 – 14.0)	12.0 (8.0 – 16.0)	7.0 (4.0 – 11.0)	0.09	10.5 (8.0 – 15.0)	12.5 (10.0 – 24.0)	16.0 (8.0 – 23.0)	0.09
WCST_CLR	76.5 (62.0 – 84.0)	72.0 (59.0 – 82.0)	76.0 (72.0 – 81.0)	0.67	71.5 (62.0 – 82.0)	67.0 (42.0 – 74.5)	57.0 (37.0 – 82.0)	0.21
WCST_CC	6.0 (6.0 – 6.0)	6.0 (5.0 – 6.0)	6.0 (6.0 – 6.0)	0.53	6.0 (6.0 – 6.0)	6.0 (2.0 – 6.0)	4.0 (1.0 – 6.0)	0.07 Post hoc L/L vs L/S 0.01
WCST_1st	12.0 (11.0 – 13.0)	12.0 (11.0 – 20.0)	11.0 (10.0 – 11.0)	0.04	11.0 (11.0 – 13.0)	37.5 (11.5 – 61.0)	12.0 (12.0 – 27.0)	0.006 Post hoc L/L vs L/S 0.002 L/S vs S/S 0.03

BMI, body mass index; WCST_P – odsetek błędów perseweracyjnych (%); WCST_NP – odsetek błędów niepersewerac yjnych (%); WCST_CLR – procent odpowiedzi zgodnych z koncepcją logiczną(%); WCST_CC – odsetek poprawnie ułożonych kategorii(%); WCST_1st – liczba kart potrzebnych do ułożenia pierwszej kategorii. Istotne różnice między podgrupami określono za pomocą testu Kruskal-Wallis ANOVA. Analiza post hoc została przeprowadzona za pomocą testu NIR Fishera..

Tabela 4. Analiza polimorfizmów DAT I wyników WCST w grupie mężczyzn w wieku ≤ 45 r.ż. I > 45 r.ż.

	Mężczyźni ≤45 (n = 36)			Mężczyźni >45 (n = 33)			
	L/L (n=24)	L/S & S/S (n=12)	P	L/L (n=14)	L/S (n=11)	S/S (n=8)	P
BMI	39.9 (36.3 – 49.2)	41.0 (36..6 – 47.6)	0.75	43.7 (33.3 – 48.9)	44.7 (30.3 – 49.1)	40.3 33.7 – 45.9)	0.84
WCST_P	9.0 (8.0 – 12.0)	9.0 (6.0 – 12.0)	0.007	12.5 (7.0 – 20.0)	14.0 (11.0 – 27.0)	13.5 (10.0 – 31.5)	0.71
WCST_NP	10.0 (5.5 – 16.0)	8.0 (4.0 – 13.0)	0.19	20.0 (18.0 – 22.0)	12.0 (5.0 – 21.0)	16.0 (14.0 – 17.0)	0.05 Post hoc Ns.
WCST_CLR	76.0 (71.0 – 83.0)	8.,0 (73.0 – 85.0)	0.12	55.0 (33.0 – 72.0)	69.0 (26.0 – 76.0)	61.5 (39.0 – 71.5)	0.91
WCST_CC	6.0 (5.0 – 6.0)	6.0 (6.0 – 6.0)	0.49	2.5 (1.0 – 6.0)	6.0 (3.0 – 6.0)	4.0 (3.0 – 5.0)	0.11
WCST_1st	12.0 (11.0 – 21.5)	12.0 (11.0 – 20.0)	0.66	19.5 (12.0 – 30.0)	11.0 (11.0 – 31.0)	17.5 (14.0 – 37.0)	0.14

BMI, body mass index; WCST_P – odsetek błędów perseweracyjnych (%); WCST_NP – odsetek błędów niepersewerac yjnych (%); WCST_CLR – procent odpowiedzi zgodnych z koncepcją logiczną(%); WCST_CC – odsetek poprawnie ułożonych kategorii(%); WCST_1^{st} – liczba kart potrzebnych do ułożenia pierwszej kategorii. Istotne różnice między podgrupami określono za pomocą testu Kruskal-Wallis ANOVA. Analiza post hoc została przeprowadzona za pomocą testu NIR Fishera.

Tabela 5. Analiza polimorfizmów DRD4 i wyników WCST w grupie kobiet w wieku ≤ 45 r.ż. i > 45 r.ż.

	Kobiety ≤45 (n = 99)			Kobiety >45 (n = 80)		
	L/L; L/S (n= 33)	S/S (n= 66)	P	L/L & L/S (n=30)	S/S (n=50)	P
BMI	40.2 (37.4 – 43.5)	42.9 (37.5 – 47.1)	0.27	44.3 (40.2 – 52.5)	43.2 (38.3 – 48.8)	0.68
WCST_P	11.0 (7.0 – 13.5)	9.0 (7.0 – 13.0)	0.07	12.0 (9.0 – 13.0)	13.0 (9.0 – 17.0)	0.09
WCST_NP	9.0 (6.0 – 14.0)	9.0 (7.0 – 14.0)	0.77	12.0 (9.0 – 20.0)	11.0 (8.0 – 18.0)	0.13
WCST_CLR	79.0 (60.5 – 84.5)	76.0 (63.0 – 84.0)	0.79	72.0 (60.0 – 81.0)	68.0 (53.0 – 82.0)	0.15
WCST_CC	6.0 (6.0 – 6.0)	6.0 (6.0 – 6.0)	0.47	6.0 (5.0 – 6.0)	6.0 (4.0 – 6.0)	0.10
WCST_1st	12.0 (11.0 – 16.0)	12.0 (11.0 – 13.0)	0.57	13.0 (11.0 – 28.0)	12.0 (11.0 – 30.0)	0.003

BMI, body mass index; WCST_P – odsetek błędów perseweracyjnych (%); WCST_NP – odsetek błędów niepersewerac yjnych (%); WCST_CLR – procent odpowiedzi zgodnych z koncepcją logiczną(%); WCST_CC – odsetek poprawnie ułożonych kategorii(%); WCST_1^{st} – liczba kart potrzebnych do ułożenia pierwszej kategorii. Istotne różnice między płcią uzyskano za pomocą testu Manna-Whitneya.

Tabela 6. Analiza polimorfizmów DRD4 I wyników WCST w grupie mężczyzn w wieku ≤ 45 r.ż. i > 45 r.ż.

	Mężczyźni ≤45 (n = 36)			Mężczyźni >45 (n = 33)		
	L/L; L/S (n=12)	S/S (n=24)	P	L/L & L/S (n=17)	S/S (n=16)	P
BMI	44.1 (38.2 – 52.5)	40.0 (3.,8 – 43.8)	0.13	44.7 (31.1 – 51.5)	41.9 (33.6 – 47.4)	0.68
WCST_P	9.5 (5.0 – 12.0)	9.0 (6.0 – 10.0)	0.82	12.0 (7.0 – 15.0)	23.5 (10.0 – 36.0)	0.06
WCST_NP	7.5 (4.5 – 11.5)	10.0 (4.0 – 19.0)	0.52	15.0 (9.0 – 18.0)	19.0 (14.5 – 21.5)	0.06
WCST_CLR	83.0 (73.5 – 85.0)	76.0 (73.0 – 86.0)	0.54	69.0 (52.0 – 76.0)	36.5 (26.5 – 67.5)	0.006
WCST_CC	6.0 (6.0 – 6.0)	6.0 (6.0 – 6.0)	0.90	5.0 (4.0 – 6.0)	2.5 (1.0 – 5.5)	0.04
WCST_1st	12.5 (10.5 – 20.5)	12.0 (11.0 – 20.0)	0.98	12.0 (11.0 – 24.0)	22.0 (11.5 – 53.5)	0.12

BMI, body mass index; WCST_P – odsetek błędów perseweracyjnych (%); WCST_NP – odsetek błędów niepersewerac yjnych (%); WCST_CLR – procent odpowiedzi zgodnych z koncepcją logiczną(%); WCST_CC – odsetek poprawnie ułożonych kategorii(%); WCST_1st – liczba kart potrzebnych do ułożenia pierwszej kategorii. Istotne różnice między płcią uzyskano za pomocą testu Manna-Whitneya.

Tabela 7. Korelacja R-Spearman'a między wiekiem, BMI i wynikami TEMPS-A u kobiet i mężczyzn.

	Kobiety (n = 178)		Mężczyźni (n = 67)	
	Wiek	BMI	Wiek	BMI
TEMPS_D	r=0,21 p=0,004 Tau Kendalla Tau= -2,74; *p*=0,006	r=-0,14 0,06	r=-0,05 p=0,68	r=0,06 p=0,63
TEMPS_C	r=-0,06 p=0,42	r=-0,16 p=0,03 Tau Kendalla Tau= -0,15; *p*=0,002	r=-0,26 p=0,03 Tau Kendalla Tau= -0,01; *p*=0,44	r=0,33 p=0,006 Tau Kendalla Tau= -0,24; *p*=0,003
TEMPS_H	r=-0,09 p=0,23	r=0,16 p=0,03 Tau Kendalla Tau= 0,01; *p*=0,37	r=0,09 p=0,46	r=-0,09 p=0,47
TEMPS_I	r=0,004 p=0,95	r=-0,07 p=0,35	r=-0,12 p=0,33	r=0,31 p=0,01 Tau Kendalla Tau= -0,13; *p*=0,05
TEMPS_A	r=0,16 p=0,03 Tau Kendalla Tau= -0,09; *p*=0,03	r=-0,11 p=0,14	r=-0,11 p=0,37	r=0,07 p=0,57

BMI – body mass index; TEMPS_D – temperament depresyjny; TEMPS_C – temperament cyklotymiczny; TEMPS_H – temperament hypertymiczny; TEMPS_I – temperament drażliwy; TEMPS_A – temperament lękowy.

Tabela 8. Analiza polimorfizmów COMT i wyników nasilenia wymiarów temperamentu w TEMPS-A w grupie badawczej.

	Wszystkie grupy (n = 245)				
	G/G (n= 64)	G/A (n= 120)	A/A (n= 61)	P	
BMI	40,9 (36,7 – 44,3)	42,5 (36,5 – 49,0)	42,4 (37,0 – 48,1)	0,52	
TEMPS_D	0,36 (0,28 – 0,42)	0,42 (0,28 – 0,52)	0,38 (0,28 – 0,43)	0,36	
TEMPS_C	0,28 (0,16 – 0,47)	0,47 (0,24 – 0,64)	0,38 (0,23 – 0,52)	0,04	Post-hoc G/G vs G/A p=0,014 G/A vs A/A ns G/Avs AA na
TEMPS_H	0,57 (0,50 – 0,67)	0,47 (0,28 – 0,61)	0,57 (0,38 – 0,57)	0,07	
TEMPS_I	0,09 (0,04 – 0,16)	0,26 (0,09 – 0,33)	0,09 (0,05 – 0,24)	0,01	Post-hoc G/G vs G/A p=0,01 G/A vs A/A ns G/Avs AA ns
TEMPS_A	0,32 (0,20 – 0,52)	0,35 (0,22 – 0,59)	0,32 (0,24 – 0,52)	0,52	

BMI – body mass index; TEMPS_D – temperament depresyjny; TEMPS_C – temperament cyklotymiczny; TEMPS_H – temperament hypertymiczny; TEMPS_I – temperament drażliwy; TEMPS_A – temperament lękowy. Istotne różnice między podgrupami zostały obliczone za pomocą testu Kruskal-Wallis'a ANOVA. Analiza post hoc została przeprowadzona za pomocą testu NIR Fishera.

Tabela 9. Analiza polimorfizmów DAT i wyników TEMPS-A w grupie badawczej.

	Wszystkie grupy (n =245)			
	L/L (n=117)	L/S (n=103)	S/S (n= 25)	P
BMI	41,2 (36,2 – 48,9)	41,6 (35,8 – 48,5)	40,7 (39,9 – 46,8)	0,90
TEMPS_D	0,42 (0,28 – 0,52)	0,38 (0,28 – 0,47)	0,38 (0,28 – 0,47)	0,71
TEMPS_C	0,38 (0,24 – 0,62)	0,38 (0,23 – 0,57)	0,33 (0,29 – 0,48)	0,86
TEMPS_H	0,52 (0,36 – 0,61)	0,52 (0,38 – 0,62)	0,57 (0,38 – 0,62)	0,87
TEMPS_I	0,19 (0,07 – 0,33)	0,14 (0,05 – 0,28)	0,09 (0,04 – 0,29)	0,23
TEMPS_A	0,32 (0,21 – 0,52)	0,33 (0,24 – 0,52)	0,44 (0,28 – 0,59)	0,41

BMI – body mass index; TEMPS_D – temperament depresyjny; TEMPS_C – temperament cyklotymiczny; TEMPS_H – temperament hypertymiczny; TEMPS_I – temperament drażliwy; TEMPS_A – temperament lękowy. Istotne różnice między podgrupami zostały obliczone za pomocą testu Kruskal-Wallis'a ANOVA.

Tabela 10. Analiza polimorfizmów genu DRD4 i wyników TEMPS-A w grupie badawczej.

	Wszystkie grupy (n = 245)		
	L/L; L/S (n=84)	S/S 114 (n= 161)	p
BMI	42,9 (38,5 – 49,0)	41,8 (37,2 – 47,1)	0,21
TEMPS_D	0,40 (0,28 – 0,47)	0,33 (0,28 – 0,47)	0,25
TEMPS_C	0,38 (0,24 – 0,61)	0,47 (0,23 – 0,57)	0,64
TEMPS_H	0,47 (0,35 – 0,59)	0,19 (0,05 – 0,28)	0,15
TEMPS_I	0,16 (0,05 – 0,33)	0,19 (0,20 – 0,55)	0,27
TEMPS_A	0,32 (0,24 – 0,47)	0,35 (0,20 – 0,54)	0,75

BMI – body mass index; TEMPS_D – temperament depresyjny; TEMPS_C – temperament cyklotymiczny; TEMPS_H – temperament hypertymiczny; TEMPS_I – temperament drażliwy; TEMPS_A – temperament lękowy. Istotne różnice między podgrupami zostały obliczone za pomocą testu Kruskal-Wallis'a ANOVA.

Tabela 11. Analiza wyników skali TEMPS-A w grupie badawczej (mediana i Q25-Q75)

	Brak zaburzeń gospodarki węglowodanowej (n=87)	IFG/IGT (n=42)	Cukrzyca (n=56)	P
TEMPS_D	0,35 (0,30 – 0,45)	0,33 (0,27 – 0,42)	0,42 (0,28 – 0,47)	0,83
TEMPS_C	0,38 (0,19 – 0,59)	0,47 (0,23 – 0,57)	0,47 (0,28 – 0,57)	0,62
TEMPS_H	0,52 (0,39 – 0,61)	0,53 (0,38 – 0,63)	0,57 (0,28 – 0,61)	0,67
TEMPS_I	0,09 (0,05 – 0,25)	0,17 (0,04 – 0,28)	0,19 (0,05 – 0,33)	0,81
TEMPS_A	0,32 (0,24 – 0,51)	0,32 (0,23 – 0,55)	0,35 (0,24 – 0,47)	0,76

Istotne różnice między podgrupami zostały obliczone za pomocą testu Kruskal-Wallis'a ANOVA. Analiza post hoc została przeprowadzona za pomocą testu NIR Fishera.

Tabela 12. Wyniki korelacji R-Spearman'a między wymiarami temperamentu afektywnego TEMPS-A a wynikami BDI i parametrów biochemicznych.

	Wyniki pacjentów z IGT/IFG			
TEMPS-A	Glukoza na czczo [mg/dl]	p	HbA1c (%)	P
Depresyjny	-0,162	0,30	-0,210	0,18
Cyklotymiczny	-0,049	0,75	-0,079	0,61
Hypertymiczny	0,327	0,03	0,126	0,42
Drażliwy	0,045	0,77	0,095	0,54
Lękowy	-0,096	0,54	0,042	0,79
BDI	0,042	0,79	-0,233	0,13
	Wyniki pacjentów z cukrzycą			
TEMPS-A	Glukoza na czczo [mg/dl]	p	HbA1c (%)	P
Depresyjny	0,455	0,0004	-0,226	0,09
Cyklotymiczny	0,274	0,04	-0,130	0,33
Hypertymiczny	-0,324	0,01	0,036	0,79
Drażliwy	-0,119	0,38	-0,257	0,055
Lękowy	0,347	0,008	0,401	0,002
BDI	0,091	0,50	0,372	0,004

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9. STRESZCZENIE W JĘZYKU POLSKIM

Otyłość to choroba związana z powikłaniami jak zaburzenia depresyjne, deterioracja poznawcza i nieprawidłowości gospodarki węglowodanowej. Wykazano rolę genów przekaźnictwa dopaminergicznego w patogenezie otyłości, a dopamina zdaje się łączyć otyłość z depresją i funkcjonowaniem poznawczym. Wciąż nie do końca poznane są korelacje polimorfizmów genów dopaminergiczych z funkcjami wykonawczymi, temperamentem afektywnym czy płcią. Brak jest też badań dotyczących roli temperamentu afektywnego w kontroli glikemii u otyłych z zaburzeniami gospodarki węglowodanowej.

W związku z powyższym w serii publikacji przyjęto następujące cele:

1. Ocena korelacji polimorfizmów genów dopaminergicznych z funkcją kory przedczołowej w populacji otyłej.
2. Analiza korelacji polimorfizmów genów dopaminergicznych z temperamentem afektywnym w populacji otyłej.
3. Ocena korelacji temperamentu afektywnego z parametrami biochemicznymi kontroli glikemii u otyłych pacjentów z cukrzycą typu 2 lub stanem przedcukrzycowym.
4. Ocena czy płeć różnicuje wyniki funkcji wykonawczych mierzonych za pomocą testu sortowania kart Wisconsin (WCST) w grupie otyłych.

Do pierwszej analizy włączono 248 osób otyłych (179 kobiet, 69 mężczyzn) Ocenę funkcji kory przedczołowej (funkcji wykonawczych) przeprowadzono za pomocą WCST. W analizie uwzględniono polimorfizmy następujących genów: *COMT*Val158Met, *DRD4* i *DAT1*.

Do drugiego badania włączono 245 osób otyłych (178 kobiet, 67 mężczyzn). Pacjentom oznaczono następujące geny przekaźnictwa dopaminergicznego: *COMT*Val158Met, *DRD4* i *DAT1*. W celu oceny temperamentu afektywnego wykorzystano autokwestionariusz Temperament Evaluation of Memphis, Pisa, Paris and San Diego (TEMPS-A).

W trzecim badaniu wzięło udział 185 pacjentów otyłych (146 kobiet, 39 mężczyzn). Po wykonaniu testu doustnego obciążenia glukozy (OGTT), pacjentów podzielono na trzy grupy: osoby obciążone cukrzycą typu 2, osoby ze stanem przedcukrzycowym i osoby bez zaburzeń gospodarki węglowodanowej. Za pomocą TEMPS-A oceniono temperament afektywny. Celem oceny kontroli glikemii, z próbki krwi oznaczono poziom hemoglobiny glikowanej 1c (HbA1c).

Wyniki pierwszej analizy ukazują pozytywną korelację między polimorfizmami genu *COMT* w przypadku allelów Met/Met i Met/Val i efektywniejszym działaniem funkcji wykonawczych w WCST, jednak wyniki utraciły istotność statystyczną w dalszej analizie. W przypadku genu *DAT1* w

grupie mężczyzn osoby z alllelami 10/10 i 10/9 uzyskały mniej błędów niepersewеracyjnych w porównaniu do homozygot 9/9. U kobiet powyżej 45 roku życia z allelem L genu *DRD4* stwierdzono lepszy wynik WCST_1$^{st.}$. Ponadto zaobserwowano istotne różnice w funkcjach wykonawczych mierzonych za pomocą WCST między mężczyznami i kobietami.

Na podstawie wyników przekaźnictwo dopaminergiczne uwarunkowane przez polimorfizmy genów dopaminergicznych zdają się wpływać na funkcje wykonawcze. Zaobserwowane różnice funkcji wykonawczych między mężczyznami, a kobietami może wynikać z działania estrogenów, które zdają się modulować przekaźnictwo dopaminergiczne.

W drugim badaniu jedynie u osób z polimorfizmem *COMT* Met/Val silniej były wyrażone temperament cyklotymiczny i drażliwy. W przypadku genów *DAT1* i *DRD4* nie stwierdzono istotnych korelacji z wymiarami temperamentu afektywnego. Uzyskane wyniki wskazują, że przekaźnictwo dopaminergiczne uwarunkowane przez allel Val/Met genu *COMT* może wiązać się z większą predyspozycją do rozwoju chorób afektywnych.

Wyniki trzeciej analizy nie wskazywały na istotne różnice temperamentu afektywnego u osób otyłych z zaburzeniami gospodarki węglowodanowej w porównaniu do grupy kontrolnej. Ocena temperamentu afektywnego w grupie osób z cukrzycą typu 2 i stanem przedcukrzycowym wykazała istotne korelaje między wymiarami temperamentu afektywnego a glukozą na czczo (FPG) i HbA1c. U osób z cukrzycą typu 2 stwierdzono pozytywną korelację między temperamentem lękowym a wartościami HbA1c, co może wskazywać na gorszą kontrolnę glikemii w tej grupie.

10. STRESZCZENIE W JĘZYKU ANGIELSKIM

Obesity is a disease associated with complications like depressive disorders, cognitive deterioration and impaired carbohydrate metabolism. Studies show that genes involed in the dopaminergic neurotransmission have significant role in the development of obesity. Dopamine is a putative factor connecting obesity with depression or cognitive deterioration. Still literature lacks information about correlations between dopaminergic gene polymorphisms and cognitive performance, affective temperament or sex. Also no studies investigated the role of affective temperament on glycemic control in obese with carbohydrate disorders.

Therefore, I established subsequent objectives of the series of publications:

1. The evaluation of correlations between dopaminergic genes polymorphisms and the executive functions in obese population.
2. The analysis of correlations between dopaminergic genes polymorphisms and affective temperament in obese population.
3. The analysis of correlations between affective temperament and biochemical parameters of glycemic control in obese with concurrent type 2 diabetes mellitus (T2DM), impaired glucose tolerance(IGT)/impaired fasting glucose (IFG).
4. The analysis whether sex differs the results of executive functions measured with Wisconsin Card Sorting Tes (WCST).

First analysis consisted of 248 obese persons (179 femals, 69 males). The evaluation of the prefrontal cortex function (executive functions) was performed with WCST. Genetic analysis included gene polymorphisms: *COMT*Val158Met, *DAT1* and *DRD4*.

Second study enrolled 245 obese subjects (178 females, 67 males). Following gene polymorphisms were evaluated: *COMT*Val158Met, *DAT1* and *DRD4*. To assess affective temperament, we utilized Temperament Evaluation of Memphis, Pisa, Paris and San Diego autoquestionnaire (TEMPS-A).

The third study enrolled 185 obese subjects (146 females, 39 males). After performing oral glucose tolerance test (OGTT), subjects were divided into three groups: obese people with T2DM, obese with IGT/IFG, and obese non-diabetic patients. Then, we evaluated affective temperament with TEMPS-A. For the assessment of glycemic control, the level of glycolated hemoglobin A1c (HbA1c) was measured from the sample of peripheral blood.

Results of the first analysis show positive correlations between *COMT* Met/Met and Met/Val polymorphisms and better results in WCST, but after further analysis those results did not

maintain statistical significant. In the group of males, subjects with *DAT1* 10/10 and 10/9 obtained less non perseverative errors compared to 9/9 homozygotes. Females who are over 45 yo and have *DRD4* L-allele gained better results of WCST_1st. We also observed significant differences between men and women regarding executive functions measured with WCST.

Obtained results suggest that dopaminergic transmission determined by dopaminergic genes polymorphisms affects the performance of prefrontal cortex. Observed dfferences in cognitive performance between men and women may result from estrogens, which may modulate dopaminergic neurotransmission.

In the second study, we observed correlations between polymorphism of *COMT* Met/Val and irritable and cyclothymic dimensions of affective temperament. Both *DAT1* and *DRD4* did not show any significant correlations with TEMPS-A. Obtained results indicate, that dopaminergic transmission modulated by *COMT* may be associated with greater susceptibility to the development of affective disorders linked with irritable and cyclothymic dimensions.

Results of the third analysis did not show any significant differences of affective temperament between obese subjects with carbohydrate disorders and non-diabetic ones. T2DM and IGT/IFG groups showed significant correlations between affective temperament and fasting plasma glucose and HbA1c values. Obese with T2DM showed positive correlation betwen anxious temperament and HbA1c, which may suggest worse glycemic control in this group.