***DRD2* and *BDNF* Polymorphisms Are Associated With Binge Eating Disorder (BED) in Patients With Weight Regain After Bariatric Surgery**

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Abstract

Objectives: Verify the frequency of polymorphisms related to obesity and Binge Eating Disorder (BED) in *DRD2* and *BDNF* genes in patients undergoing bariatric surgery with weight regain above 10% of the weight lost.

Methods: Evaluation of 177 individuals undergoing bariatric surgery with weight regain, divided into two groups: Group 1: individuals with BED; Group 2: individuals without BED. The individuals were submitted to anthropometric evaluation, analysis of the presence of BED using a validated questionnaire, and blood collection for genotyping of the polymorphisms, *rs6265* (*BDNF*) and *rs1800497* (*DRD2*). The Kolmogorovi-Smirnov, t-test, chi-square, Mann Whitney, Pearson correlation were used for statistical analysis.

Results: *CC* genotypes for *rs1800497* polymorphism, and *GG* for *rs6265* polymorphism were more frequent in patients without the disorder. The presence of at least one *T* allele (*DRD2*) and at least one *A* allele (*BDNF*) was more frequent in patients with BED. The combination of *AA* + *GA* + *TT* + *TC* genotypes prevailed in patients with the disorder.

Conclusions: The *CC* (*DRD2*) and *GG* (*BDNF*) genotypes suggest protection for patients against BED, while genotypes that have at least one *T* allele (*DRD2*) and one *A* allele (*BDNF*) suggest greater risk and appear to act in synergism.

Level of evidence: III (evidence obtained from case-control analytic study).

Introduction

Binge eating disorder (BED) is one of the most common eating disorders, being characterized by recurrent episodes of binge eating that occur at least once a week for three months, associated with lack of control and pronounced suffering. Binge eating episodes are generally associated with aspects such as eating faster than normal, eating more than gastric capacity, eating in large quantities in the absence of physical hunger, and feeling guilty about binge eating, compromising physical and psychosocial health significantly [1–3]. However, this disorder is not associated with inappropriate compensatory strategies after binge eating, which is why BED is often associated with obesity [1, 4–5]. The prevalence of BED is estimated at 2 to 3.5% and is observed in 5 to 30% of individuals with obesity [2–3].

The etiology of binge eating disorder (BED) is multifactorial, involving genetic, psychological, and sociocultural factors. Among the genetic aspects, we highlight the single nucleotide polymorphisms (SNP), which are examples of genetic modifications, which can significantly influence the regulation of neural circuits that control the appetite/satiety pathway, as well as the regulation of cerebral reward systems [2, 5]. Although SNPs are not the only determining factors, they indicate a genetic predisposition for the individual to develop metabolic disorders [6].

Several genes can be associated with overweight and eating disorders [7]. An example is the *DRD2* gene (dopamine D2 receptor), which encodes the dopamine receptor type D2 [8]. This receptor is in the presynaptic membrane of dopaminergic neurons and has the function of modulating the release of dopamine in the synaptic cleft in the reward system of the dopaminergic pathways [9]. The SNP *rs1800497* is associated with disorders such as binge eating [10]. Since the presence of one or two copies of this polymorphism is related to the reduction in the density of D2 receptors in the mesolimbic areas of the reward system, which suggests that individuals with reduction of this regulatory receptor tend to present behaviours that stimulate the release of dopamine [11], as well as in the use of drugs of abuse [12] and in the binge eating [13].

Another gene of interest is the *BDNF* (brain-derived neurotrophic factor) gene, which plays an important role in regulating weight, appetite, and satiety by stimulating the release of hormones such as somatostatin, the thyrotrophin-releasing hormone (TRH) and the corticotrophin-releasing hormone (CRH) in the hypothalamus [8, 14]. The presence of the *rs6265* polymorphism has been associated with eating disorders and obesity in different populations [15–16]. Other SNPs present in this gene, such as *rs925946*, *rs10501087* and *rs988712*, may also be related to genetic determinants of overweight and obesity [17].

Obesity is a complex multifactorial disease, related to the excessive accumulation of fat that can cause health problems. It is estimated that 1.9 billion adults are overweight in the world, 650 million of whom are obese [18]. There are several risk factors for obesity, among them: genetic factors, from which several markers related to susceptibility to overweight, family history, psychological aspects and socio-cultural and economic context have been identified. In addition, obesity is associated with several other diseases such as depression, type 2 diabetes, cardiovascular disease, cancer, and others [19].

Among the various treatments for obesity control, the traditional ones are the first choice for the patient, which consist of lifestyle changes, associated with eating and physical exercise. There are also surgical methods, including gastric bypass, a procedure performed as a

treatment to control severe obesity based on the patient's body mass index (BMI), the presence of comorbidities and time of previous clinical treatment [20].

The average weight loss due to bariatric surgery is 60 to 75% of excess weight. However, weight regain is observed substantially in many patients, after a few years of surgery. Several studies show that after 24 months weight regain begins, with a weight gain observed in 28.1% of the patients, reaching 41% after 10 years of the surgical procedure, indicating that the regain is progressive in the long term [21–24].

Weight regain is a complex, multifactorial mechanism, and is related to several factors such as lifestyle, mental health, hormones, surgical technique, inadequate diet [25], alcohol consumption [26] and physical inactivity [27]. Together, eating disorders, which are often observed in bariatric patients, can significantly impact the outcome of bariatric surgery, and may be another contributing factor to weight regain [28].

In this context, given the important participation of genetic factors in the development of obesity and eating disorders, and considering that this is a disease that affects millions of individuals worldwide, leading to incapacitation and consequent damage also to public coffers, it is made necessary to elucidate molecular mechanisms involved with obesity to apply personalized medicine. Thus, the objective of the study was to verify the frequency of SNPs related to obesity and binge eating present in the *DRD2* and *BDNF* genes in patients with weight regain in the postoperative period of bariatric surgery who have or not binge eating disorder (BED).

Materials And Methods

Were evaluated 177 individuals aged 18 to 65 years, of mixed race, of both sexes, with recurrence greater than 10% of the total weight lost, after bariatric surgery. The individuals were monitored by the Bariatric Surgery Outpatient Clinic of the Clinical Hospital of the Ribeirao Preto Medical School (HCFMRP) and the Base Hospital of Sao Jose do Rio Preto and were divided into two groups: Group 1 (G1) - patients with BED; Group 2 (G2) - patients without BED. The study was approved by the Research Ethics Committee of the Sao Jose do Rio Preto Medical School (FAMERP) (CAAE number 65678117.7.0000.5415) and by the Research Ethics Committee of the Ribeirao Preto Medical School of the University of Sao Paulo (Process 14375/2018), and all participants signed the Free and Informed Consent Form (FICF). Patients under 18 or over 65 with a history of liver disease were excluded from the study; anticoagulated or with coagulation disorders; pregnant women; severe malnourished, anemic, chronic alcohol users or drug users; with a history of recent neoplasia; reoperated or with immediate or late postoperative complications.

Anthropometric measurements (height (A), body weight (P) and body mass index (BMI) were performed at three specific times: before surgery (P1); two years after surgery (P2), and more than 5 years after surgery (P3) Peripheral blood was also collected for genetic analysis of the SNPs and the Binge Eating Scale (BES) was applied [29], for patient distribution in the studied groups (G1 and G2) according to the score in the questionnaire, patients with scores less than or equal to 17 were allocated to G2 (without BED) and patients above 17 points were allocated to G1 (with BED).

Anthropometric assessment

For anthropometric assessment, the following indicators were used: weight, height, BMI and weight regain (%). The patients were weighed on a Filizola® digital scale, platform type, with a capacity of 300 kg and precision of 0.2 kg. To measure height, a vertical nail with a 0.5 cm graduation was used. The BMI was obtained using the formula $BMI = W / H^2$, for the three weighing periods (W1, W2 and W3); to calculate the percentage of weight regain (WR), the formula $WR = 100 \times (P3 - P2) / (P1 - P2)$; to calculate the ideal weight (IW), that is, $BMI = 25 \text{ Kg} / \text{m}^2$, $IW = 25 \times H^2$; to calculate the current excess weight (EW), the formula $EW = W3 - IW$.

Genetic analysis

DNA extraction from the peripheral blood sample was performed with a GE Healthcare kit (Illustra blood genomic Prep Mini Spin kit), according to the supplier's guidelines, using 200µL of the extracted material. Subsequently, the DNA was eluted in water and the concentration adjusted to 50µg/µL, with the aid of the Qubit 2.0 spectrophotometer (Invitrogen®). After this analysis, they were stored at -80 ° C in aliquots, aiming at stability and preservation of the DNA, thus avoiding the degradation of the material. DNA genotyping for analysis of *rs1800497* SNP of the *DRD2* gene and *rs6265* SNP of the *BDNF* gene was performed by Real-Time Polymerase Chain Reaction (RT-PCR), using the 7500 Fast - Applied Biosystems® equipment. Genotyping was performed using the TaqMan Pre-Designed SNP Genotyping Assays kit (Applied Biosystems, Foster City, CA), following the manufacturer's standards.

Statistical Analysis

The normality of data distribution was verified by the Kolmogorov-Smirnov test, the descriptive statistics was composed of mean and standard deviation values. Mann Whitney's post hoc test t analysis was applied to verify differences between groups. The odds ratio was

calculated to check the odds ratio for BED in selected patients. Correlation analysis between genetic and anthropometric variables were performed using Pearson's correlation coefficient. Allele and genotype frequencies were analysed using the Chi-square or Fisher's tests. The Hardy-Weinberg equilibrium calculation was performed which evaluates if allele and genotype frequencies in a population will remain constant from one generation to next generation in the absence of disturbing factors. Statistical significance (p-value) was established at $p < 0.05$. The analysis was performed using the Statistical Package for Social Science software (SPSS version 20.0 [Inc. Chicago. IL]).

Results

Table 1 presents the sociodemographic and anthropometric data of patients with obesity who underwent bariatric surgery and had a weight regain $> 10\%$ in the postoperative period ($N = 177$), distributed in groups with BED ($N = 94$) and without BED ($N = 83$). The analysis showed that the groups with and without BED did not differ from each other for all assessed variables ($p > 0.05$). The female gender prevailed in both groups (89% and 81% for the groups with and without BED, respectively), with no statistically significant difference between them ($p = 0.136$). The mean age did not differ between the groups, being 41.0 ± 9.6 years for the group with BED and 41.2 ± 10.5 years for those without the disorder ($p = 0.901$). Regarding weight and BMI, a significant reduction in these variables was noted when comparing the pre-surgery periods and after weight loss in the post-surgery period, for both groups ($p < 0.01$). On the other hand, the percentage of weight regain for the BED group was 22.02% and 25.93% for the group without the disorder ($p = 0.471$).

Table 1
Sociodemographic and anthropometric data of patients with and without Binge Eating Disorder (BED).

Variables	With BED (a)						Without BED (b)						Value <i>p</i>
	N = 94						N = 83						
<i>Sociodemographic</i>	N		%				N		%				
Female	84		89				67		81				0,136
Male	10		11				16		19				
	Pre-surgery (c)		Post-surgery (minimum weight) (d)		Post-regain (e)		Pre-surgery (f)		Post-surgery (minimum weight) (g)		Post-regain (h)		
<i>Anthropometric</i>	M	SD	M	SD	M	SD	M	SD	M	SD	M	SD	
Height	1.63	0.083	-	-	-	-	1.63	0.088	-	-	-	-	0.716
Age	41.02	9.65	-	-	-	-	41.30	10.57	-	-	-	-	0.901
Regain (%)	22.02	15.22	-	-	-	-	26.32	34.14	-	-	-	-	0.471
Ideal weight	66.22	6.79	-	-	-	-	67.13	7.22	-	-	-	-	0.732
Overweight	26.15	15.07	-	-	-	-	29.31	19.21	-	-	-	-	0.426
Weight	133.4	22.94	83.49	15.45	92.57	16.52	132.4	27.26	86.48	19.62	94.24	20.75	##
BMI	49.41	7.32	31.00	5.54	34.64	5.86	49.05	8.20	31.69	6.28	35.40	7.71	##
T test; ANOVA; Fisher's test; a) With disorder; b) Without disturbance; c) pre-surgical weight with disorder; d) minimum post-surgical weight with disorder; e) weight after regain with disorder; f) pre-surgical weight without disorder; g) minimum post-surgical weight without disorder; h) weight after recurrence without disorder; P-value = significance level for $p < 0.05$; M = mean; SD = standard deviation; BMI = Body Mass Index; N = number; ## p-values for the evaluated analyzes: weight: cxf = 0.737; dxg = 0.336; exh = 0.636; cxd = < 0.01 ; cxe = < 0.01 ; dxe = < 0.01 ; fxg = < 0.01 ; fxh = < 0.01 ; gxh = < 0.01 ; BMI: cxf = 0.758; dxg = 0.452; exh = 0.556; cxd = < 0.01 ; cxe = < 0.01 ; dxe = < 0.01 ; fxg = < 0.01 ; fxh = < 0.01 ; gxh = < 0.01 ;													

There was no significant difference in weight comparison for groups with and without BED in the preoperative ($p = 0.737$), postoperative ($p = 0.336$) and after regain ($p = 0.636$) periods. The same occurred for the BMI variable, showing that the groups studied (with and without BED) are homogeneous for these indicators.

Table 2 shows the genotype and allele frequency of the *rs1800497* polymorphism for the *DRD2* gene in patients with and without BED. In this case, it was found that the *CC* genotype was more frequent in patients without BED (67.5%), when compared to the group with BED (44.7% $p = 0.004$); On the other hand, the presence of the *CT* genotype (48.9%) and T allele (0.31) were prevalent in the BED group compared to the

group without the disease (27.7% and 0.19, respectively; $p = 0.006$ and $p = 0.012$), showing its possible risk character for the disorder. In addition, the presence of at least one T allele was favourable to binge eating (55.5%; $p = 0.004$).

Table 2
Genotype and allele frequency of *rs1800497* polymorphism for *DRD2* gene in patients with and without Binge Eating Disorder (BED)

<i>DRD2</i> polymorphism (<i>C > T</i>)	With BED		Without BED		Value p (OR/CI)
Genotypes	N = 94		N = 83		
	N	%	N	%	
<i>CC</i>	42	44.7	56	67.5	0.004
					0.38/(0.21–0.71)
<i>CT</i>	46	48.9	23	27.7	0.006
					2.50/(1.33–4.68)
<i>TT</i>	6	6.4	4	4.8	0.751
					1.34/(0.36–4.94)
Total	94	100	83	100	0.004
<i>_T</i>	52	55.3	27	32.5	2.56/(1.30–4.70)
Alleles	N	Abs. Freq.	N	Abs. Freq.	
<i>C</i>	130	0.69	135	0.81	0.012
<i>T</i>	58	0.31	31	0.19	0.51/(0.31–0.84)
Total	188	1	166	1	
Fisher's exact test or χ^2 ; OR = Odds Ratio; CI = Confidence Interval; p value = significance level for $p < 0.05$; Abs freq = Absolute Frequency; N = number					

Figure 1 shows the frequency for each genotype represented in Table 2, in which it is possible to verify that the genotype frequency *CC* is higher in patients without BED, the genotype *CT* is more common in patients with BED, as well as the presence of at least one *T* allele ($p < 0.05$ for all these combinations).

Table 3 shows the genotypic and allele frequency of the *rs6265* polymorphism for the *BDNF* gene in patients with and without BED. Thus, it was observed that the *GG* genotype and *G* allele were prevalent in patients without BED (81.9% and 0.91 respectively) when compared to the group with BED (66% and 0.82, respectively; $p = 0.017$ and 0.020), showing a possible protective character for the disorder. The *GA* and *_A* genotypes prevailed in the group with the disorder (33% and 34%) compared to the group without the disorder (18.1 and 18%; respectively; $p = 0.026$ and 0.025), possibly favouring the appearance of BED. On the other hand, the frequency of the *G* allele was protective for BED ($p = 0.020$).

Table 3

Genotype and allele frequency of *rs6265* polymorphism for the *BDNF* gene in patients with and without Binge Eating Disorder (BED)

<i>BDNF</i> polymorphism (<i>G > A</i>)	With BED		Without BED		Value <i>p</i> (OR/CI)
Genotypes	N = 94		N = 83		
	N	%	N	%	
<i>GG</i>	62	66.0	68	81.9	0.017
					0.42/(0.21–0.86)
<i>GA</i>	31	33.0	15	18.1	0.026
					2.23/(1.10–4.51)
<i>AA</i>	1	1.1	0	0	1.000
					2.67/(0.10–66.7)
Total	94	100	83	100	0.025
χ^2	32	34	15	18	2.34/(1.10–4.70)
Alleles	N	Abs. Freq.	N	Abs. Freq.	
<i>G</i>	155	0.82	151	0.91	0.020
<i>A</i>	33	0.18	15	0.09	0.46/(0.24–0.89)
Total	188	1	166	1	
Fisher's exact test or χ^2 ; OR = Odds Ratio; CI = Confidence Interval; P-value = significance level for $p < 0.05$; Abs freq = Absolute Frequency; N = number					

Figure 2 shows the frequency for each genotype represented in Table 3, where it is possible to verify that the *GG* genotype frequency is higher in patients without BED, the *GA* genotype is more common in patients with BED, as well as the presence of at least one allele *A* ($p < 0.05$ for all these combinations).

Table 4 shows the genotypic combinations for the evaluated polymorphisms (*rs1800497* from the *DRD2* gene and *rs6265* from the *BDNF* gene). In this case, it was observed that the combination of genotypes with at least one T allele for the *rs1800497* polymorphism and one A allele for the *rs6265* polymorphism was more frequent in those patients with BED (18%) compared to the group without the disorder (7%; $p = 0.002$), pointing out that in synergism these two polymorphisms can predispose to binge disorder.

Both groups were within the Hardy-Weinberg balance ($p > 0.05$) for the *DRD2* ($\chi^2 = 0.225$) and *BDNF* ($\chi^2 = 2.089$) polymorphisms.

Table 4

Genotypic combination for the *DRD2* gene *rs1800497* and the *BDNF* gene *rs6265* polymorphisms in patients with and without Binge Eating Disorder (BED)

Variables	With BED		Without BED		Value <i>p</i> (OR/CI)
	N = 94		N = 83		
	N	%	N	%	
<i>AA + GA + TT + TC</i>	17	18	6	7	0,002
<i>GG + CC</i>	27	29	47	57	4.93/(1.73–14.01)
Fisher's exact test or χ^2 ; OR = Odds Ratio; CI = Confidence Interval; p value = significance level for $p < 0.05$; N = number					

When the mean values and standard deviations of the BMI were analyzed in relation to the presence of the genotypes of the studied polymorphisms, it was observed that there was no statistically significant difference between the groups with and without the disorder, with $p > 0.05$ for all studied genotypes. (Table 5).

Table 5
Mean values and standard deviations of the BMI of patients with and without Binge Eating Disorder (BED) in relation to the genotypes for the *DRD2* gene rs1800497 and the *BDNF* gene rs6265 polymorphisms

Variables	With BED				Without BED				Value p	
	Pre-surgery (a)		Post-regain (b)		Pre-surgery (c)		Post-regain (d)		axc	bx d
	M	SD	M	SD	M	SD	M	SD		
<i>DRD2</i>										
<i>CC</i>	49.17	7.80	35.07	6.05	48.34	7.36	36.28	8.64	0.657	0.535
<i>CT</i>	49.50	7.28	34.50	5.70	47.33	9.00	33.87	5.77	0.349	0.725
<i>TT</i>	50.5	4.42	33.00	6.60	-	-	-	-	-	-
<i>_/T</i>	49.61	6.98	34.30	5.75	47.25	8.70	33.81	5.58	0.268	0.777
<i>BDNF</i>										
<i>GG</i>	49.68	7.31	35.40	5.64	48.40	7.75	35.31	8.14	0.421	0.960
<i>GA</i>	48.39	6.96	32.78	5.70	46.4	8.09	35.70	6.38	0.455	0.202
<i>AA</i>	-	-	-	-	-	-	-	-	-	-
<i>_/A</i>	48.91	7.45	33.29	6.11	46.4	8.09	35.70	6.38	0.368	0.308
ANOVA test with post-test Tukey; p value = significance level for $p < 0.05$; M = Mean; SD = Standard Deviation.										

The analysis carried out between BMI values and the patients' scores on the BES revealed a positive correlation between the referred variables ($r = 0.320$; $p = 0.015$).

Correlation between BMI and BED ($r = 0.320$; $p = 0.015$).

Discussion

In this study, the presence of genotypes with at least one *_ / T* allele for the *rs1800497* SNP of the *DRD2* gene, and *_ / A* for the *rs6265* SNP of the *BDNF* gene were more prevalent in patients with BED. These data corroborate with other studies, which also show an association of these polymorphisms with the disease [10, 30–31]. It is known that the presence of these polymorphisms, especially the *rs1800497* in *DRD2* gene, is associated with reduced dopamine function in the brain [32–33] by about 30 to 40% of the normal value [5]. In addition, they seem to be related to increased BMI and eating disorders in women with bulimia spectrum disorder [34–35], being considered a possible marker for high risk of developing pathological eating behavior [36]. In addition, other studies show that the presence of the *T* allele for the *DRD2* gene is associated with unhealthy eating, abnormal levels of glucose and triglycerides [37], other addictive behaviors combined with overweight [38], obesity [39], hedonic diet [40], and high sensitivity to reward [41], which directly influences the increase in caloric intake [42]. However, it is important to note that these variables were not evaluated in this study.

The findings of the present study show that the presence of at least one *T* allele was prevalent in patients with obesity associated with BED, as compared to the control group (with obesity and without BED). Therefore, the presence of at least one *T* allele was favorable to binge eating ($p = 0.004$). This result corroborates with the literature that points to a higher prevalence of the *rs1800497* SNP of the *DRD2* gene among individuals with the disorder [10, 30]. This prevalence supports the view that this eating disorder may be related to hypersensitivity to the reward, this polymorphism being a predisposition favored by facilitated access to highly palatable and caloric foods [30]. On the other hand, another study, also comparing groups with obesity with and without BED, found the prevalence of the *T* allele in the group without the disorder [43], while another found no significant difference between the groups [44], showing that the results are conflicting.

Still regarding the *DRD2* gene polymorphism, it is reported in the literature that the *TT* genotype is associated with increased body fat and increased adiposity compared to the *CT* and *CC* genotypes [33]. However, the low frequency of the referred genotype in the present study can be considered a limitation, mainly due to its sample size. Therefore, it was not possible to evaluate its effect. In addition, there was no correlation between pre-surgical and post-surgical BMI for patients with and without BED for each of the analyzed genotypes (Table 5).

As for the SNP *rs6265* of the *BDNF* gene, studies have shown that the presence of polymorphism is associated with obesity [15, 45], as well as overweight in childhood [46–48]. The present study showed a predominance of the *GA* genotype in individuals with BED ($p = 0.025$), revealing that the presence of at least one *A* allele can be an aggravating factor for BED (Odds Ratio: 2.34; Confidence Interval: 1, 10 – 4.7; $p = 0.025$). However, another study involving three groups of patients (bulimia nervosa, BED and healthy controls), all female, revealed that in the BED group, individuals with the *AA* genotype exhibited a significantly greater severity of binge eating than those with *GA* and *GG* genotype [49]. The analysis in the present study for the *AA* genotype was not possible because only one patient had such a genotype.

In another study, they analyzed the interaction of the *rs6265* SNP of the *BDNF* gene and sex. Thus, men with the *GG* genotype had higher BMI, waist circumference, and weight than those with *GA* or *AA*. On the other hand, women with the *GG* genotype had a significantly lower BMI than those with *GA* or *AA*. Thus, the *rs6265* SNP of the *BDNF* gene is associated with the risk of obesity in different ways according to sex [15]. A study conducted only with female patients found an association between obesity and the presence of the *A* allele [31]. Another study conducted with female patients did not find differences in genotype frequency between the groups with or without BED [44]. However, the present study did not carry out an analysis to investigate the predominance of the genotype between the sexes, due to the prevalence of females in 85% of the sample. However, it is important to note that in the present series, the *GG* genotype proved to be a protective factor for obesity (Odds Ratio: 0.42; Confidence interval: 0.21–0.86; $p = 0.017$) and the *GA* genotype, aggravating factor (Odds Ratio: 2.23; Confidence interval: 1.10–4.51).

The analysis combining genotypes of the two studied polymorphisms revealed that the presence of at least one *T* allele for the *DRD2* gene polymorphism (*rs1800497*) and an *A* allele for the *BDNF* gene polymorphism (*rs6265*) were predominant in the BED group ($p = 0.002$). The literature evaluating the combination of these polymorphisms is scarce, however in view of the data obtained in this study, a possible synergism was observed between these genetic variants, since the function of both genes is related to the addiction of chemical substances such as alcohol and cocaine [50–52], psychiatric disorders [53–54] and eating disorders [38, 49].

Weight regain was present in both groups of obese patients with or without BED. However, there was no difference in the mean BMI between the groups for each of the studied genotypes. The literature on weight regain for the polymorphisms studied is scarce, however, a study revealed that no effect was detected on the presence of *rs6265* SNP of the *BDNF* gene and weight gain throughout life in patients followed from 40 to 70 years of age [55]. In addition, a study that followed 1406 patients for more than six years after bariatric surgery revealed that more than 67% of patients recover 20% or more of the weight lost in the first two years [23]. In this context, obesity is characterized as a multifactorial disease, and the evidence presented by the literature indicates that even after different types of treatments for weight loss (surgical or not), a regain occurs over the years. Thus, several factors, including genetics, can act for this "new" weight gain after treatments.

The presence of the two polymorphisms studied (*rs1800497* SNP of the *DRD2* gene, and *GG* for *rs6265* SNP of the *BDNF* gene) suggest that there may be a reduction in gene expression for both genes and pre-disposition to binge eating. The presence of the *rs1800497* SNP of the *DRD2* gene has been associated with a reduction in the density of type 2 dopamine receptors in the presynaptic membrane of the mesolimbic pathways, causing an increase in the concentration of dopamine in the synaptic cleft and contributing to behavior of abuse and compulsion [13]. The *rs6265* SNP of the *BDNF* gene was related to the decrease in the production of neurotrophins that act in the hypothalamus and stimulate the production of hormones related to satiety such as TRH and CRH [14].

The strength of this study is related to the significant association of the evaluated polymorphisms and BED. The literature addressing this association is scarce and in the present study, even with a reduced sample, it was possible to observe this effect. On the other hand, the main limitation of this study refers to the small sample size. However, this factor was not limiting enough to show the association of the studied polymorphisms both independently and in synergism. In addition, the absence of a eutrophic group can also be considered a limitation. Since studies involving the frequency of these SNPs with BED in eutrophic individuals are also scarce or nonexistent in the literature. Fact that could assist in elucidating the prevalence of these genetic variants in eutrophic casuistry.

Conclusion

In conclusion, the *CC* genotypes for the *DRD2* gene *rs1800497* and *GG* for the *BDNF* gene *rs6265* polymorphisms seem to protect patients from this BED case series, due to their higher prevalence in the group without the disease. On the other hand, the presence of at least one *T* allele (*DRD2*) and at least one *A* allele (*BDNF*) confers a higher risk for the development of BED. The combination of the referred genotypes (*AA + GA + TT + TC*) of the evaluated polymorphisms is associated with the presence of the disorder. Weight regain is similarly frequent for both groups. In addition, the BMI of patients with and without the disorder do not correlate with the different genotypes of the evaluated polymorphisms, showing that weight regain appears to have a multifactorial character.

What is already known on this subject?

There is no consensus in the literature on the presence of the studied polymorphisms (rs1800497 SNP of the *DRD2* gene and rs6265 SNP of the *BDNF* gene) in individuals with obesity and BED.

What this study adds?

This study adds that the presence of genotypes with at least one *_ / T* allele for the *rs1800497* SNP of the *DRD2* gene, and *_ / A* for the *rs6265* SNP of the *BDNF* gene were more prevalent in patients with BED and obesity, suggesting a possible synergism between these genetic variants and additional risk for BED.

Declarations

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Conflicts of interest/Competing interests

The authors declare no conflict of interest. The funders had no role in the design of the study; in the collection, analysis, or interpretation of data; in the writing of the manuscript, or in the decision to publish the results.

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Figures

Figure 1

Genotype frequency of the rs1800497 polymorphism for the DRD2 gene in patients with and without Binge Eating Disorder (BED). * = $p < 0.05$

Figure 2

Genotype frequency of the rs6265 polymorphism for the BDNF gene in patients with and without Binge Eating Disorder (BED). * = $p < 0.05$

Figure 3

Correlation between BMI and BED ($r = 0.320$; $p = 0.015$)