DRD2 and *BDNF* Polymorphisms Are Associated with Binge Eating Disorder in Patients with Weight Regain After Bariatric Surgery

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Research Article

Keywords: binge eating disorder, polymorphism, obesity, bariatric surgery, weight regain.

Posted Date: July 29th, 2021

DOI: https://doi.org/10.21203/rs.3.rs-334784/v2

Abstract

Aim: To analyze the association and susceptibility of Single Nucleotide Polymorphisms (SNPs) in the DRD2 and BDNF genes with BED in patients with weight regain in the postoperative period of bariatric surgery.

Methods: 177 individuals who underwent bariatric surgery with weight regain were evaluated and divided into two groups according to the BED diagnostic. The individuals were submitted to an 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) by Real-Time Polymerase Chain Reaction (RT-PCR). Results: the presence of wild-type alleles for rs1800497 (CC) and rs6265 (GG) were more frequent in patients without BED. Nevertheless, the presence of one or two variant alleles for rs1800497 (CT+TT) and rs6265 (GA+AA) was more frequent in patients with BED. The combination of the two studied SNPs prevailed in patients with BED.

Conclusions: In the presence of polymorphisms rs1800497 in the DRD2 gene and rs6265 in the BDNF gene, isolated and/or combined could occur an additional risk for the development of BED in patients with obesity, especially in the context of weight regain.

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

Introduction

Binge eating disorder (BED) is characterized by recurrent episodes of binge eating at least once a week for three months, associated with lack of control and pronounced suffering. Binge eating episodes are generally associated with eating faster than normal, more than gastric capacity, large quantities in the absence of physical hunger, and feeling guilty about binge eating, compromising physical and psychosocial health [1–3]. However, since BED is not usually associated with compensatory behaviors, such as fasting and excessive exercise after eating, BED individuals are frequently obese [1, 4–5]. Indeed, the prevalence of BED in individuals with obesity is about 5 to 30% [2–3].

BED etiology is multifactorial, involving psychological, sociocultural, and, more recently, genetic factors. Single Nucleotide Polymorphism (SNP) is a genetic variation that influences the regulation of neural circuits in the control of the appetite/satiety pathway and the regulation of cerebral reward systems [2, 5]. Although SNPs are not the only determinant factors, they indicate a genetic predisposition for the individual to develop eating disorders [6].

Several genes can be associated with obesity and eating disorders [7]. An example is a gene of dopamine D2 receptor (DRD2), which encodes the dopamine receptor type D2 [8–9]. The SNP rs1800497 into this gene is associated with binge eating [10]. Another gene is the brain-derived neurotrophic factor (BDNF), which regulates weight gain, appetite, and satiety [8, 11]. The SNP rs6265 into the BDNF gene has been associated with eating disorders and obesity in different populations [12–13]. Other SNPs in this gene, such as rs925946, rs10501087, and rs988712, may also be related to genetic determinants of overweight and obesity [14].

Obesity is a complex multifactorial disease related to the excessive accumulation of fat and health problems. Approximately 1.9 billion adults are overweight, and 650 million are obese worldwide [15]. Obesity is associated with genetic factors, family history, psychological, socio-cultural, and economic aspects [16]. The treatment of obesity is also complex. Even with the success of bariatric surgery for weight loss, in the long term, weight regain may occur. Eating disorders, which are often observed in bariatric patients, are important factors that significantly impact the outcome of bariatric surgery, contributing to weight regain [20].

In this context, given the importance of genetic factors in the development of obesity and eating disorders and considering the magnitude of these health problems worldwide, understanding the associated mechanisms involved in this process becomes necessary. Thus, the present study aimed to analyze the association and susceptibility of SNPs in the DRD2 and BDNF genes with BED in patients with weight regain in the postoperative period of bariatric surgery.

Materials And Methods

Ethical Statement

All procedures followed in this study have been performed in accordance with the ethical standards as laid down in the Declaration of Helsinki. The study protocol was approved by the Ethics Committee of the Sao Jose do Rio Preto Medical School, Brazil (CAAE number 65678117.7.0000.5415) and by the Ethics Committee of the Ribeirao Preto Medical School at the University of Sao Paulo, Brazil (Process 14375/2018). Informed consent was obtained from all individual participants.

Study population

We evaluated 177 individuals aged 18 to 65 years, of mixed race, 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. According to the Binge Eating Scale (BES) score, subjects were divided into two groups: with BED and without BED. Patients under 18 or over 65 years; using anticoagulants or with coagulation disorders; pregnant women; malnourished or anemic; alcoholic or drug users; with neoplasia; reoperated or with postoperative complications were not included in the study.

Study procedures

Anthropometric measurements, height (H), body weight (W), and body mass index (BMI) were performed at three specific times: preoperative, two years after surgery, and > 5 years after surgery, according to the last medical appointment of each patient. Peripheral blood samples were collected for SNPs genotyping. The (BES) was applied two years after surgery and the period > 5 years after surgery [21].

Anthropometric assessment

We measured the H and W for BMI calculation, and weight regains (WR) (%). For W, a Filizola® digital scale, platform type, with a capacity of 300 kg and precision of 0.2 kg, was used. To measure H, 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 periods (preoperative [W1], two years after surgery [W2] and > 5 years after surgery [W3]); the percentage of WR (%) was calculated using the formula WR = 100 × (> 5 years after surgery - two years after surgery) / (preoperative - two years after surgery); to calculate the ideal weight (IW): $BMI = 25 Kg / m^2$, $IW = 25 \times H^2$; to calculate the current excess weight (EW): 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 (*data not shown*). The continuous variables were described as mean and standard deviation. The student's t-test analyzed the difference between groups. The odds ratio (OR) was calculated to check relative risk for BED in selected patients. Correlation analysis between BES score and IMC was performed using Pearson's correlation coefficient. The genotype and allele frequency analysis were performed using Fisher's exact test or Chi-square test. The Hardy-Weinberg equilibrium calculation was performed to evaluate if allele and genotype frequencies in a population will remain constant from one generation to the next generation in the absence of disturbing factors. RStudio software was used for Linear Regression analysis and to verify the relationship between the polymorphisms studied with the disease (adjusted for sex and age). The power calculation to achieve the gene-environment interaction was performed using the software Quanto version 1.2.4 (University of Southern, 2009, California, USA), considering the allele frequency of rs1800497 polymorphism for *DRD2* gene and Binge Eating Disorder prevalence (0.31 and 0.53, respectively). For a desired power of 80% and a significance of 0.05, the calculated sample size required was 171. 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 weight regain > 10% in the postoperative period (N = 177), distributed in groups with BED (n = 94) and without BED (n = 83). Each group was analyzed in three periods: preoperative, postoperative, post-regain. The student's t-test analysis showed that the groups with and without BED did not differ 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), and we did not find differences 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 decrease in these variables was noted when comparing the preoperative with the postoperative period for both groups ($p < 0.01$). The percentage of weight regain was similar for the BED group (22.02%) and the group without BED (25.93%) ($p = 0.471$).

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 regaining ($p = 0.636$) periods. The same occurred for the BMI, showing that both groups are homogeneous for these indicators.

Table 2 shows the genotype and allele frequency of the SNP rs1800497 in the *DRD2* gene in patients with and without BED. We found that the CC genotype, the homozygous wild type, was more frequent in patients without BED (67.5%) when compared to the group with BED (44.7% $p = 0.004$); Nonetheless, the presence of the one or two variant alleles (CT + TT) was more frequent in the BED group (55.3%) compared to the group without BED (32.5%) ($p = 0.004$), indicating a possible risk for BED related with this polymorphism.

Table 3 shows the genotypic and allele frequency of the SNP rs6265 in the *BDNF* gene in patients with and without BED. We observed that the homozygous wild type, GG, was more frequent in patients without BED (81.9%) when compared to the group with BED (66%) (p = 0.017), demonstrating a possible protective role for the disorder. The presence of the one or two variant alleles (GA + AA) prevailed in the group with the disorder (34%) compared to the group without the disorder (18.1%) (p = 0.025), possibly favoring the appearance of BED.

The genotypic combinations for the SNPs rs1800497 (DRD2) and rs6265 (BDNF) are shown in **Table 4**. We observed that the combination of rs1800497 and rs6265 was more frequent in patients with BED (18%) compared to the group without BED (7%) (p = 0.002), indicating that in synergism, these polymorphisms could predispose the individuals to binge disorder. Both groups were within the Hardy-Weinberg balance (p > 0.05) for the DRD2 (X^2 = 0.225) and BDNF (X^2 = 2.089) polymorphisms.

When the BMI was analyzed in the presence of the polymorphism's genotypes, we did not observe differences between groups with and without BED (**Table 5**). However, the analysis of BMI and the patients' scores on the BES revealed a positive correlation between the referred variables (r = 0.320; p = 0.015).

Finally, we performed a linear regression analysis to verify the relationship between the SNPs variables (rs6265 - BDNF and rs1800497 DRD2) with the presence or absence of BED adjusted for gender and age. The analysis did not indicate a relationship between patients without BED and polymorphisms (adjusted by: DRD2 gender: y = 1.68–0.01x, p = 0.99; and age: y = 1.80–0.01x, p = 0.71; BDNF gender: y = 1.85–0.02x, p = 0.82, and age: y = 1.53 + 0.01x, p = 0.06). The same occurred for patients with BED (DRD2: y = 1.23 + 0.13x, p = 0.5216; BDNF: y = 1.83 -0.16x, p = 0.32). However, we found a relationship between polymorphism for BDNF and age (y = 1.01 + 0.001x, p = 0.03) in patients with the disorder. In general, each increase in age (in years) increases the chance of having the disorder in the presence of the BDNF polymorphism.

Discussion

The SNP rs1800497 in 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 dopamine concentration contributing to behavior of abuse and compulsion [13]. The SNP rs6265 in the BDNF gene decreases the production of neurotrophins that acts in the hypothalamus and stimulates hormones related to satiety, such as TRH and CRH [11]. Interestingly, in the present study, the SNP rs1800497 in the DRD2 gene and the SNP rs6265 in the BDNF gene were more frequent in patients with BED, corroborating with previous studies, which also found an association between these polymorphisms and BED [10, 22–23].

Especially for the SNP rs1800497 in the DRD2 gene, studies have demonstrated reduced dopamine function in the brain [24–25], about 30 to 40% of the normal value [5]. In addition, this polymorphism was linked to increased BMI and eating disorders in women with bulimia spectrum disorder [26–27], which is considered a possible marker for the high risk of developing pathological eating behavior [28]. Other studies showed that the presence of the T allele for the DRD2 gene is associated with unhealthy eating, abnormal levels of glucose and triglycerides [29], other addictive behaviors combined with overweight [30], obesity [31], hedonic diet [32], and high sensitivity to reward [33]. All these factors directly influence the increase in caloric intake [34] favored by facilitated access to highly palatable and caloric foods [22].

The presence of the SNP rs6265 in the BDNF gene has been associated with obesity [12, 36] and overweight in childhood [37–39]. The present study showed a predominance of a variant allele (GA + AA) in individuals with BED

(p = 0.025), revealing that the presence of the A allele can be an aggravating factor for BED. Another study involving three groups of female patients (bulimia nervosa, BED, and healthy controls) revealed that in the BED group, individuals with the AA genotype exhibited a significantly greater severity of binge eating [40]. In another study, the interaction between the rs6265 SNP and sex indicated that men with the GG genotype had higher BMI, waist circumference, and weight than those with GA or AA genotypes. Nonetheless, women with the GG genotype had a significantly lower BMI than those with GA or AA genotypes. According to the authors, the rs6265 SNP in the BDNF gene is associated with an increased risk of obesity in a sex manner [12]. In the present study, we did not analyze the predominance of the genotype between the sexes due to the higher prevalence of females in the sample.

The analysis combining genotypes of the two studied polymorphisms revealed that polymorphism rs1800497 in the DRD2 gene and the polymorphism rs6265 in the BDNF gene were predominant in the BED group. The literature evaluating the combination of these polymorphisms and BED is scarce. However, given the data obtained in this study, a possible synergism could occur between these genetic variants potentiating the predisposition to develop BED disorders [30, 40, 44, 45].

Weight regain was present in both groups of obese patients with and without BED. However, there was no difference in the mean BMI between the groups for each studied genotype. The literature on weight regains for the polymorphisms studied is limited. Perkovic et al., 2013 did not find an association between SNP rs6265 and weight gain throughout the life of patients followed from 40 to 70 years of age [46]. 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 lost weight in the first two years [47–48]. 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 weight regain could occur over the years. Thus, several factors, including genetics, can act for this "new" weight gain after treatments.

The strength of this study is 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. In addition, the absence of a non-obese group could also be considered a limitation. Also, the correction for ethnicity could not be applied due to our study considered an admixed population.

Conclusion

In conclusion, the presence of polymorphism rs1800497 in the DRD2 gene and rs6265 in the BDNF gene, isolated and/or combined, indicated a higher risk for the development of BED in patients with obesity, especially in the context of weight regain. In addition, the BMI of patients with and without BED was not correlated with the SNPs, showing that weight regain appears to have a multifactorial character.

Declarations

What is already known on this subject?

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

What does this study add?

In the presence of polymorphisms rs1800497 in the DRD2 gene and rs6265 in the BDNF gene, isolated and/or combined could occur an additional risk for the development of BED in patients with obesity, especially in the context of weight regain.

Funding

This research was supported by São Paulo Research Foundation (FAPESP) (#grants numbers: 2020/08687-9, 2018/24069-3, 2018/08784-4, and 2013/12819-4].

Conflicts of interest/Competing interests

The authors declare no conflict of interest. The funders had no role in the study's design, 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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Tables

Table 1

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

Variables	**With BED**			**Without BED**			**p-value**
	N = 94			N = 83			
Sociodemographic	N	%		N	%		
Female	84	89		67	81		0.136
Male	10	11		16	19		
	Preoperative (a)	Postoperative (b)	Post-regain (c)	Preoperative (d)	Postoperative (e)	Post-regain (f)	
Anthropometric	M ± SD	M ± SD	M ± SD	M ± SD	M ± SD	M ± SD	M ± SD
Height	1.63 ± 008	-	-	1.63 ± 0.08	-	-	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[a]	92.57 ± 16.52[a,b]	132.4 ± 27.26	86.48 ± 19.62[d]	94.24 ± 20.75[d,e]	
BMI (kg/m²)	49.41 ± 7.32	31.00 ± 5.54[a]	34.64 ± 5.86[a,b]	49.05 ± 8.20	31.69 ± 6.28[d]	35.40 ± 7.71[d,e]	

T-test; p-value = significance level for $p < 0.05$; a = When compared with Preoperative with BED; b = When compared with Postoperative with BED; c = When compared with Post-regain with BED; d = When compared with Preoperative without BED; e = When compared with Postoperative with BED; f = When compared with Post-regain without BED; M = mean; SD = standard deviation; BMI = Body Mass Index; N = number.

Table 2

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

DRD2 polymorphism (C > T)	**With BED**		**Without BED**		**p-value (OR/CI)**
Genotypes	N = 94		N = 83		
	N	%	N	%	
CC	42	44.7	56	67.5	0.004
					0.38/(0.21–0.71)
CT	46	48.9	23	27.7	0.006
					2.50/(1.33–4.68)
TT	6	6.4	4	4.8	0.751
					1.34/(0.36–4.94)
Total	94	100	83	100	0.004
CT + TT	52	55.3	27	32.5	2.56/(1.30–4.70)
Alleles	N	Abs. Freq.	N	Abs. Freq.	
C	130	0.69	135	0.81	0.012
T	58	0.31	31	0.19	0.51/(0.31–0.84)
Total	188	1	166	1	

Fisher's exact test or X^2; p value = significance level for $p < 0.05$; OR = Odds Ratio; CI = Confidence Interval; Abs. FrEq. = Absolute Frequency; N = number.

Table 3

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

BDNF polymorphism (G > A)	With BED		Without BED		p-value (OR/CI)
Genotypes	N = 94		N = 83		
	N	%	N	%	
GG	62	66.0	68	81.9	0.017
					0.42/(0.21–0.86)
GA	31	33.0	15	18.1	0.026
					2.23/(1.10–4.51)
AA	1	1.0	0	0	1.000
					2.67/(0.10–66.7)
Total	94	100	83	100	0.025
GA + AA	32	34	15	18.1	2.34/(1.10–4.70)
Alleles	N	Abs. Freq.	N	Abs. Freq.	
G	155	0.82	151	0.91	0.020
A	33	0.18	15	0.09	0.46/(0.24–0.89)
Total	188	1	166	1	

Fisher's exact test or X^2; p-value = significance level for $p < 0.05$; OR = Odds Ratio; CI = Confidence Interval; Abs. FrEq. = Absolute Frequency; N = number.

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		p-value (OR/CI)
	N = 94		N = 83		
	N	%	N	%	
AA + GA + TT + TC	17	18	6	7	0.002
GG + CC	27	29	47	57	4.93/(1.73–14.01)

Fisher's exact test or X2; p-value = significance level for $p < 0.05$; OR = Odds Ratio; CI = Confidence Interval; N = number.

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.

	With BED		Without BED		p-value	
Variables	Preoperative (a)	Post-regain (b)	Preoperative (c)	Post-regain (d)	axc	bxd
DRD2	M ± SD	M ± SD	M ± SD	M ± SD		
CC	49.17 ± 7.80	35.07 ± 6.05	48.34 ± 7.36	36.28 ± 8.64	0.657	0.535
CT	49.50 ± 7.28	34.50 ± 5.70	47.33 ± 9.00	33.87 ± 5.77	0.349	0.725
TT	50.5 ± 4.42	33.00 ± 6.60	-	-	-	-
CT + TT	49.61 ± 6.98	34.30 ± 5.75	47.25 ± 8.70	33.81 ± 5.58	0.268	0.777
BDNF	49.68 ± 7.31	35.40 ± 5.64	48.40 ± 7.75	35.31 ± 8.14	0.421	0.960
GG	48.39 ± 6.96	32.78 ± 5.70	46.40 ± 8.09	35.70 ± 6.38	0.455	0.202
GA	-	-	-	-	-	-
AA	48.91 ± 7.45	33.29 ± 6.11	46.40 ± 8.09	35.70 ± 6.38	0.368	0.308
GA + AA						

T-test; p-value = significance level for $p < 0.05$; M = Mean; SD = Standard Deviation; axc = When compared Preoperative with BED (a) versus preoperative without BED (c); bxd = When compared Post-regain with BED (b) versus Post-regain without BED (d)