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ORIGINAL ARTICLE

Analysis of Factors Associated with Outcomes of Bariatric Surgery: rs1800497 ANKK1, rs1799732 DRD2 Genetic Polymorphisms, Eating Behavior, Hedonic Hunger, and Depressive Symptoms

Steven Daza-Hernández[1] · Elva Pérez-Luque[1] · Claudia Martínez-Cordero[2] · Nicté Figueroa-Vega[1] · Mónica I. Cardona-Alvarado[1] · Norberto Muñoz-Montes[2]

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Abstract

Introduction A therapeutic approach to severe obesity is bariatric surgery (BS), which is considered an effective intervention for ameliorating comorbidities such as T2DM, hypertension, dyslipidemia, and cardiovascular diseases. Some polymorphisms are considered markers for addictive disorders and hedonic hunger. We analyzed factors associated with the outcomes of BS, including rs1800497 *ANKK1* and rs1799732 *DRD2* polymorphisms, eating behavior, hedonic hunger, and depressive symptoms.

Methods We retrospectively selected 101 patients who underwent BS and agreed to participate. The previous conditions to BS, such as body mass index (BMI), systolic blood pressure (SBP), diastolic blood pressure (DBP), and comorbidities, were registered; the scholarship value was evaluated as the total number of years of scholarly education. To evaluate the post-surgery conditions of the participants, we took blood samples, anthropometric measures, and 3 questionnaires to evaluate eating behavior (TFEQ-R18), hedonic hunger (PFS), and depressive symptoms (PHQ-9). The *ANKK1* rs1800497 and rs1799732 *DRD2* polymorphisms were genotyped.

Results The median total weight loss (TWL) was 34.7 kg, with a BMI of 33.8 kg/m^2, 6 (4–8) years after BS. The TWL was positively associated with the TFEQ-R18 score ($p = 0.006$) and negatively associated with triglycerides ($p = 0.011$). rs1800497 *ANKK1* was associated with TFEQ-R18 (OR = 1.13 (1.02–1.25), $p = 0.009$). We also found a negative correlation of pre-surgery BMI with scholarship ($r = -0.27$, $p < 0.05$).

Conclusion The patients showed an improvement in metabolic and anthropometric parameters post-surgery. Interestingly, the *ANKK1* Taq1A polymorphism was associated with eating behavior and scholarship with pre-surgery BMI, which may be considered predictors of BS outcomes.

Keywords Obesity · Bariatric surgery · DRD2 polymorphisms · Eating behavior · Depressive symptoms

Introduction

The World Health Organization defined obesity as abnormal or excessive fat accumulation that presents a risk to health and is considered a risk factor for chronic illnesses such as type 2 diabetes mellitus (T2DM), high blood pressure dyslipidemia, cardiovascular diseases (CVD), respiratory disease, and joint disorders.[1] These comorbidities could be ameliorated or even in remission after BS.[2] Several therapeutic approaches, such as dietary education, lifestyle modification, physical exercise, and psychological support, have been used for obesity treatment.[3] Nevertheless, weight loss and glycemic control are difficult to maintain in the long term.[4,5] Another alternative is BS, which is considered the most effective intervention for severe obesity (BMI ≥ 40 kg/m^2 or ≥ 35 kg/m^2 with comorbidities).[6]

There are different surgical methods for obesity treatment; popular surgical methods are Roux-en-Y gastric bypass (RYGB), sleeve gastrectomy (SG), mini-gastric bypass, and biliopancreatic diversion (BPD). However,

✉ Elva Pérez-Luque
elvaleticiaperez@yahoo.com

[1] Departamento de Ciencias Médicas, Universidad de Guanajuato, Campus León, León, Mexico

[2] Hospital Regional de Alta Especialidad del Bajío, León, Guanajuato, Mexico

some studies have reported that 20–30% of patients do not achieve satisfactory weight loss post-BS.[4,7] Furthermore, another study reported that one-fifth of patients undergoing BS may not lose enough weight to be considered successful.[8] Several factors associated with unsuccessful weight loss have been described, such as behavioral problems, social and demographic factors, surgery techniques, and genetic polymorphisms. Additionally, advanced age, higher initial BMI, and T2DM are predictors of minor weight loss following RYGB.[9,10]

Eating patterns (such as binging) and depression are most frequently associated with poor outcomes.[11] The main question in this area is to evaluate whether there are relations between overeating and food craving with addictive behavior related to the mechanisms of reward.[12] The rewarding nature of food mediated via the dopaminergic system can be empowered under conditions of excessive stress, triggering a vicious cycle leading to overconsumption of palatable food and obesity.[13]

The association of dopamine D2 receptor (DRD2) with the development of obesity has been reported.[14,15] The low availability of dopamine receptors in patients with obesity may be considered the mechanism for the development of obesity by the dopamine receptor gene.[16] Considering the crucial role of dopamine in the brain reward circuit and its involvement in food behavior, it is important to analyze genetic variants that affect the availability and secretion of dopamine.[17] One gene most studied related to addiction vulnerability includes the ankyrin-repeat kinase domain containing 1 gene (ANKK1), which is located on 11 chromosomes, comprises 8 exons, and codes for a 765 amino acid protein that acts as a serine/threonine kinase.[18] Specifically, the *ANKK1* TaqIA (rs1800497) polymorphism consists of a single cytosine (C, A2 allele) to thymine (T, A1 allele) change, which causes a glutamine to lysine substitution. This single-nucleotide polymorphism (SNP) affects dopamine receptor availability,[19] which has been associated with the risk of alcohol dependence and severe alcoholism,[20–22] and to date, *ANKK1* TaqIA is considered a current marker for addictive disorders.[23] Some studies report an association between TaqIA polymorphisms and obesity, body mass index, and food intake.[12,24,25] The *ANKK1* TaqIA polymorphism is also associated with a higher food consumption frequency of unhealthy food groups.[26] Another rs1799732 polymorphism located in *DRD2* results in the insertion (Ins) or deletion (Del) of cytosine at position -141 in the promoter region of the *DRD2* gene. The -141 C Del allele has been associated with reduced promoter activity, resulting in decreased *DRD2* protein expression[27]. Controversial results have been found for rs1799732 *DRD2*, while a study found no association of this polymorphism with binge eating disorder[28,29]; another report showed a significant association with BMI and hedonic hunger.[17] On the other hand, rs1799732 *DRD2* shows significant interaction with the State-Trait Anxiety Inventory (STAI) scale in e-cigarette users.[30] These data show that genetic loci may interact with obesity treatments and influence the weight loss outcome.

Therefore, identifying genetic factors related to weight loss after bariatric surgery could help to guide weight management strategies pre- and post-surgery and to identify and develop novel interventions.[31] The objective of this study was to analyze factors associated with the outcomes of bariatric surgery, including rs1800497 *ANKK1,* rs1799732 *DRD2* genetic polymorphisms, eating behavior, hedonic hunger, and depressive symptoms.

Material and Methods

Subjects

We performed a retrospective analysis of the information contained in the medical files of patients from the surgery service of a public hospital who underwent Roux-en-Y gastric bypass (RYGB) only from May 2010 to November 2021 to collect the basal conditions to bariatric surgery, such as weight, body mass index (BMI), systolic blood pressure (SBP), diastolic blood pressure (DBP), comorbidities, hypertension, dyslipidemia, diabetes, and scholarship, which were registered in years as elementary education (6 years), middle and high school (3 years), bachelor (3 years), and university (5 years). The maximum scholarship value corresponds to the total number of years of scholarly education. One hundred sixty-nine patients were found as a result of scrutiny; from them, 101 agreed to participate in the study post-surgery, 78 women and 23 men. All participants were fully informed of the aims of the study and were asked to sign informed consent to participate. The study was carried out according to the ethical standards of the Declaration of Helsinki (1983) and in agreement with the Good Clinical Practice guidelines. The study was approved by the Institutional Ethics Committee of the University (CIBIUG-P70-2020) and by the Investigation Committee of the Hospital (CEI-36–2020).

Post-surgery Procedure

The patients were quoted at 8 AM after an overnight fast. Personal and clinical data were registered, anthropometric measurements were taken, and blood pressure (BP) was measured. Weight was measured with a Roman-type Tanita BC533 scale, and height was measured using a SECA 406 Stadiometer to calculate BMI. Systolic and diastolic blood pressures were measured in a sitting position after ten minutes of rest. All measurements were conducted in duplicate. Venous blood samples were taken after overnight fasting for

the measurement of serum glucose and lipid profiles and for DNA extraction. Serum glucose, lipid, and hepatic profiles were measured using enzymatic methods with a chemical analyzer.

Questionnaires

During the interviews, three questionnaires were administered post-surgery to all patients. Eating behavior was assessed using the Three-Factor Eating Questionnaire with 18 items (TFEQ-R18), which is a valid instrument to measure eating behavior in individuals with normal weight, as in individuals with obesity.[32,33] This instrument contains 3 dimensions (scales): (1) dietary restraint, (2) disinhibition, and (3) perceived hunger, and it is qualified with a scale from 0 to 100.[32,33] Depressive symptoms were evaluated with the Patient Health Questionnaire (PHQ-9), which evaluates the presence and severity of depressive symptoms according to the criteria of the Handbook Diagnostic and Statistical of Mental Disorders; the PHQ-9 generates a scale from 2 to 27, and a score of up to 5 suggests the presence of depressive symptoms.[34,35] The Power Food Scale questionnaire (PFS) has a score scale from 1 to 5, where a major score indicates major motivation to consume appetizing food; this questionnaire has been validated to measure hedonic eating behavior.[36]

Genotyping of ANKK1 TaqIA rs1800497 and rs1799732 DRD2 Polymorphisms

DNA was extracted from peripheral blood leucocytes according to the TSNT protocol and quantified using the NanoDrop system (Roche). The genetic variants of the dopaminergic pathway *ANKK1 TaqIA* rs1800497 and rs1799732 *DRD2* were genotyped using a validated Taqman® allelic discrimination protocol (ThermoFisher Scientific® Waltham, MA, USA). All samples were analyzed with a CFX96 Touch Thermalcycler (Bio-Rad) using the recommended cycling conditions: (1) denaturation phase (95 °C for 10 min) followed by annealing (95 °C for 15 s) and extension for 40 cycles (60 °C for 1 min). To check the reliability of genotyping, 10% of the samples were reanalyzed, and 99% matching was obtained.

Statistical Analysis

The normality of the distribution of data was assessed by the Kolmogorov−Smirnov test. The Hardy–Weinberg equilibrium was assessed for both polymorphisms. We used descriptive statistics to present the data as medians (25–75 quartiles). To compare groups, we used the Mann–Whitney or Kruskal–Wallis test. Chi-square or Fisher's exact test was used to compare categorical variables. Spearman's correlation analysis was performed between scholarship and pre-BMI. The association of total body weight loss (TBWL) with metabolism and genotypes of SNPs was evaluated with a multiple regression analysis. Logistic regression analysis was used to assess the association of the *ANKK1* TaqIA rs1800497 polymorphism with pre-surgery glucose levels, TBWL, and the TFEQ-R18 questionnaire score. Analyses were carried out using the statistical Statistica 7 package (Statsoft Inc., Tulsa, OK, USA), and $p < 0.05$ was considered significant.

Results

A total of 101 patients from the surgery service of a public hospital agreed to participate in the study 6 (4 - 8) years after surgery. Table 1 shows the comparison of age, weight, BMI, blood pressure, and glucose levels pre- and post-surgery. The TWL was 34.7 kg, %TWL was 23%, and %EBWL was 58.5, suggesting that BS helps to lose approximately 50% of excess weight. We also found a negative correlation between scholarship and pre-surgery BMI ($r = -0.27$, $p < 0.05$), which means that more years of study of participants led to lower pre-BMI levels. The scores of the applied questionnaires were as follows: TFEQ-R18 56.9 (50.4–63.7); PFS 2.19 (1.7–2.6); and PHQ-9 5.5 (2 - 11).

The distribution of frequencies of rs1800497 *ANKK1* and rs1799732 *DRD2* polymorphisms is in equilibrium according to the Hardy–Weinberg equilibrium (Table 2). Table 3 shows the comparison of anthropometrics, metabolic variables, and questionnaire scores according to genotypes of the rs1800497

Table 1 Comparison of anthropometric and clinical variables at baseline and post-surgery

Variable	Basal	Post-surgery	*Z*; *p*
Age (years)*	42 (34–48)	47 (40–54)	
Weight (kg)	121 (108–140)	82.7 (73.3–103)	7.47; $p < 0.00001$
BMI (kg/m^2)	47.1 (42.7–54.6)	33.82 (29.1–38.8)	5.08; $p < 0.00001$
SBP (mmHg)	125 (116–130)	122 (112–132)	0.52; NS
DBP (mmHg)	70 (70–80)	74 (60–80)	2.90; $p = 0.0037$
Glucose (mg/dl)	94 (87–106)	88 (84–95)	3.11; $p = 0.001$
TWL (kg)		34.7 (22.9–48.9)	
%TWL		23 (16.6–33)	
%EBWL		58.5 (40–79)	
Ideal weight (kg)		64 (58.5–68.9)	

Data are shown as the median with 25–75 quartiles. *Mean ± SD. *BMI*, body mass index; *SBP*, systolic blood pressure; *DBP*, diastolic blood pressure; *TWL*, total weight loss; *%TWL*, percent total weight loss; *%EBWL*, percent excess body weight loss. Wilcoxon's test: *Z*; *p* statistical significance level; *NS* not significant

Table 2 Distribution of frequencies of the polymorphisms

	Frequency of genotypes $N=101$ (%)	Allele	Frequency allelic	X^2; p
rs1800497 *ANKK1 (TaqIA)*				
A2A2 (CC)	28 (27.72)	C	0.50	1.19; NS
A2A1 (CT)	45 (44.55)	T	0.50	
A1A1 (TT)	28 (27.72)			
rs1799732 *DRD2*				
CC	53 (52.47)	C	0.75	3.39; NS
C/Del	45 (44.55)	Del	0.25	
Del/Del	3 (2.97)			

C, cytosine; *T*, thymine; *Del*, deletion; *NS*, not significant. X^2 and p values corresponding to the Hardy–Weinberg equilibrium

ANKK1 polymorphism under the codominant model. Our results show that pre-surgery glucose and TFEQ-R18 scores were higher in patients with the rs1800497 TT genotype (double variant), and post-surgery triglyceride levels were marginally higher than those in patients with other genotypes. The genotypes of polymorphism rs1800497 of the *ANKK1* gene under the dominant or recessive model were analyzed, but no associations were found. No significant differences in the comparison of analyzed parameters among the genotypes of the rs1799732 *DRD2* polymorphism under codominant, dominant, and recessive models were found.

For multiple regression analysis, we designed a model that included glucose pre-surgery, total cholesterol and actual triglyceride levels, the polymorphism rs1800497 *ANKK1* under the codominant model, and scores of the PFS, TFEQ-R18, and PHQ-9 questionnaires as independent variables and TWL as dependent variables. A negative association of actual triglyceride levels and a positive association with TFEQ-R18 scores but no association with rs1800497 *ANKK1* polymorphisms were found. Similar results were found using the same model and only changed the rs1799732 *DRD2* polymorphism (Table 4).

To confirm the data in Table 3, we used a logistic regression model that included pre-surgery glucose, total weight loss (TWL), and TFEQ-R18 score to analyze the association of the rs1800497 *ANKK1* polymorphism with these variables. Under the dominant model, rs1800497*ANKK1* showed a significant association only with the TFEQ-R18 score in carrier individuals of A2A1 and A1A1 genotypes (with one or two allelic variants) of this polymorphism OR = 1.13 (1.02–1.25, $p=0.009$).

Conclusion

In this work, we analyzed the outcomes of bariatric surgery by evaluating the TWL and factors that may influence it, such as genetics, eating behavior, hedonic hunger, and depressive symptoms, in a sample of 101 patients from the surgery service of a public hospital who underwent bariatric surgery. In this group, the median pre-surgery weight was 121 kg, which is between the USA (140 kg) and Sweden (119.2 kg) populations. The pre-surgery BMI in several reports fluctuated from 42.5 to 50.2 kg/m^2[24,5,37–39] in our

Table 3 Comparison of anthropometrics, biochemistry, and metabolic variables according to genotypes of the rs1800497 *ANKK1* polymorphism

Variable	A2A2 ($n=28$) CC $n=28$	A1A2 ($n=45$) CT $n=45$	A1A1 ($n=28$) TT $n=28$	H; p
Pre-weight (kg)	121 (106–141)	121 (108–136)	120 (110–144)	NS
Pre-BMI (kg/m^2)	46.5 (43–53.3)	47 (42.8–52.8)	51.1 (41.2–55.9)	NS
Post-BMI (kg/m^2)	33.3 (29.6–38.7)	33 (29–38.8)	35.6 (30–39.8)	NS
Pre-surgery glucose (mg/dl)	91 (86–106)	91 (85–96)	102 (96–116)	8.5; 0.01
TWL	35.9 (18.7–42)	37.3 (24.2–49.4)	31.6(23–54.79)	NS
% TWL	24.8 (14–37.9)	23.9(19.2–33)	23 (16.2–30.9)	NS
% EWL	57.3 (38–78.5)	62.7 (47.8–73.9)	53.7 (39.3–78.6)	NS
Post-surgery glucose (mg/dl)	90 (84–94)	86 (83–96)	88.5 (84–96)	NS
Post-surgery HDL-Chol (mg/dl)	53 (41.5–60)	53 (45–60.5)	54 (47.5–64.5)	NS
Post-surgery total Chol (mg/dl)	157 136–179)	150 (131–171)	156 (126–177)	NS
Post-surgery triglycerides (mg/dl)	90 (69–147)	88 (70–108)	108 (86–145)	4.9; 0.08
Post-surgery PFS	2.38 (1.78–2.66)	1.92 (1.66–2.47)	2.11 (1.76–2.59)	NS
Post-surgery TFEQ-R18	53.4 (49–58.6)	57.7 (52.5–64.6)	62 (51.7–67.2)	7.2; 0.02
Post-surgery PHQ-9	5.0 (1.5–8)	5.0 (1.5–10.5)	7.5 (2–17.5)	NS

Data are presented as the median (25–75). *BMI*, body mass index; *TWL*, total weight loss; *%TWL*, percent total weight loss; *%EWL*, percent excess weight loss; *%EBMIL*, percent excess BMI loss; *HDL-Chol*, HDL-cholesterol; *total Chol*, total cholesterol; *PFS*, Power Food Scale; *TFEQ-R18*, Three-Factor Eating Questionnaire; *PHQ-9*, Patient Health Questionnaire. Comparison using the codominant model. The Kruskal–Wallis test: H; *NS*, not significant

Table 4 Multiple regression analysis for the rs1800497 *ANKK1* and rs1799732 *DRD2* polymorphisms using total weight loss (TWL) as the dependent variable

Variable	Beta	Error standard beta	*T*-value	*p*-value
Pre-surgery glucose (mg/dl)	−0.159	0.131	−1.214	NS
Post-surgery total Chol (mg/dl)	0.226	0.140	1.61	NS
Post-surgery triglycerides (mg/dl)	−0.349	0.150	−2.31	0.011
rs1800497 *ANKK1* polymorphism	−0.122	0.148	−0.826	NS
PFS	0.016	0.141	0.116	NS
TFEQ-R18	0.424	0.149	2.84	0.006
PHQ-9	0.201	0.149	1.344	NS
	Beta	Error standard beta	*t*-value	*p*-value
Pre-surgery glucose (mg/dl)	−0.160	0.128	−1.24	NS
Post-surgery total Chol (mg/dl)	0.224	0.138	1.62	NS
Post-surgery triglycerides (mg/dl)	−0.389	0.147	−2.64	0.011
rs1799732 *DRD2* polymorphism	−0.163	0.128	−1.28	NS
PFS	0.085	0.133	0.636	NS
TFEQ-R18	0.363	0.137	2.63	0.011
PHQ-9	0.155	0.144	1.07	NS

Post-surgery total Chol, total cholesterol; *PFS*, Power Food Scale; *TFEQ-R18*, Three-Factor Eating Questionnaire; *PHQ-9*, Patient Health Questionnaire. Comparison using the dominant model. *NS*, not significant

group and was 47.1 kg/m^2. The median age at BS in the Mexican population was 41 years in a previous report, and in our group, the median age was 42 years.[37,38] Additionally, it has been reported that the %TWL following bariatric surgery (20–25%) within the first 3 years[40,41] in our group reached 23 (6.6–33%) at 6 years post-BS.

Female gender participation fluctuates between 61 and 80%; in our group, 77% were women. These data suggest that more women sought BS in the forty decades. In our work, RYGB induced remission of T2DM in 82% of patients and hypertension remission in 78% of post-surgery patients, and only one patient did not lose weight at 6 years after BS. In previous studies, T2DM remitted in 62% of patients at 6 years and 60% at 1 year.[42–44] Interestingly, we found a negative correlation of pre-surgery BMI with scholarship ($r = -0.27$, $p < 0.05$). This relationship has not been previously explored and requires verification since in our study group, 49% of participants had a university education. Nevertheless, the patients had satisfactory results in weight loss,[42] %EWL,[38] and %TWL[43] and important remission of T2DM and hypertension but did not reach their ideal weight. Our data still show clinical variability in outcomes after RYGB in patients.

Depressive symptoms and mood disorders are commonly seen among patients with severe obesity; in fact, patients who seek treatment for obesity have higher rates of depression than patients with obesity who are not seeking intensive weight management.[45] In addition, changes in depressive symptoms were significantly related to changes in BMI ($r = 0.42$; $p < 0.0001$).[45] Health-related quality of life and depressive symptoms significantly improve after surgery[46,47] and reduce the overall prevalence of depression.

The term food addiction is used in the sense of psychological dependence as a personality trait that is unable to deal psychologically with continuous opportunities to eat, and this could reflect addiction and obesity analogous to drug abuse that is characterized by a decrease in dopamine D2 receptor (DRD2), which has been interpreted as evidence of decreased dopaminergic activity.[27] In addition, the Taq1A polymorphism (rs1800497) has been associated with a 30–40% lower number of DR2D receptors and predicts low D2 receptor availability in healthy volunteers,[48] which may also have a critical role. We investigated the D2 receptor genes, specifically the *DRD2* (rs1799732) and *ANKK1* (rs1800497) polymorphisms, in a group of subjects who underwent bariatric surgery to explain differences in weight, eating behavior, and hedonic hunger after BS. The frequency of the A1 allele in our population was 50%, and similar results were obtained in West Mexican regions, such as Nayarit (51%) and Jalisco (47%).[21] Allele A1 is associated with obesity,[17,49] hedonic hunger,[17] and binge eating disorder[28] and was also associated with a higher risk of abnormal glucose, triglycerides, and VLDL levels in Mexican subjects.[26] Patients with binge eating episodes (BED) homozygous for the A1 allele of rs1800497*ANKK1* exhibited a significant association with BED (OR = 7.69; 95% CI 2.08–29.4; $p = 0.001$).[50] A previous study reported that *ANKK1*Taq1A polymorphisms may influence children's eating behavior, which may lead to children compensating for hypodopaminergic function with palatable foods.[29]

These findings have shown on the one hand, in the comparison between the different genotypes of rs1800497*ANKK1*, that the carriers of the A1A1 (variant double) genotype had higher pre-surgery glucose levels

and post-surgery TFEQ-R18 scores. On the other hand, the dominant model, rs1800497*ANKK1* showed a significant association with the TFEQ-R18 score in those carrier individuals of A2A1 and A1A1 genotypes, OR = 1.13 (1.02–1.25, $p = 0.009$). These data confirmed the association of the TFEQ-R18 score with polymorphic variants of rs1800497*ANKK1*, which means that individuals with higher TFEQ-R18 scores may have worse eating behavior. We also found an association of total weight loss (TWL) with the TFEQ-R18 score and with triglyceride levels. However, we did not find an association of TWL with this polymorphism.

In our study, we found no association for the rs1799732 *DRD2* polymorphism. According to our results, no association of rs1799732 *DRD2* with food intake and anthropometric parameters has been detected[29] or with binge eating.[28] However, it has been reported to be associated with BMI, hedonic hunger,[17] and increased risk of MetS.[51]

This work presents several limitations. The small sample size probably influenced the TWL not showing a direct association with rs1800497 *ANKK1* but through the TFEQ-R18 score. In addition, we carried out only two evaluations of the patients, pre-surgery and post-surgery 6 (4–8 years), and therefore we do not have data on the changes in BS outcomes at a short time (6 or 12 months, per example) that allows us to know changes in the lifestyle of patients at several times/points after BS, which would impact the answers to the questionnaires.

In conclusion, at 6 years after bariatric surgery, the patients maintained a %EWL of 58.5%. Total weight loss (TWL) was negatively associated with post-surgery triglycerides and positively associated with TFEQ-R18 scale scores. In addition, the TFEQ-R18 score was significantly associated with the rs1800497 *ANKK1* polymorphism (OR = 1.13 (1.02–1.25, $p = 0.009$), which indicates an interaction between the *ANKK1*Taq1A polymorphism and eating behavior. We also found a negative relationship between scholarly education and pre-surgery BMI, which can influence the outcome of bariatric surgery; it could influence the outcome of bariatric surgery.

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