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Influence of the Brain-Derived Neurotrophic Factor Gene Polymorphism on Weight Loss Following Intragastric Balloon Intervention: A Cross-Sectional Study

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Background and Aim: There is noticeable heterogeneity in weight loss outcomes following intragastric balloon (IGB) treatment, with average weight loss ranging between 11% to 15% of total body weight. Genetic variations associated with obesity have been found to influence weight loss response, however such variations are limited. Therefore, the aim of this study is to investigate the impact of the obesity associated *brain-derived neurotrophic factor (BDNF)* gene polymorphism rs11030104 with weight loss outcomes following IGB treatment.

Methods: In this cross-sectional study, *BDNF* rs11030104 was analysed in 106 individuals who underwent intragastric balloon treatment. Weight loss metrics were evaluated at the three-month follow-up: percentage of total weight loss (%TWL), percentage of excess weight loss (%EWL), and percentage of body mass index loss (%EBMIL). The effects of additive and dominant genetic models were evaluated. Both linear and logistic regression were applied to assess associations between rs11030104 genotypes and weight loss metrics.

Results: A total of 71 participants completed the 3-month follow-up assessment (loss to follow-up: 33%). This study found a significant association between the *BDNF* rs11030104 polymorphism and weight loss. A-allele carriers showed a better response to IGB treatment. Individuals carrying the AA genotype were found to have a greater %TWL than those carrying the GG genotype at 3 months post-IGB treatment (11.05% vs 5.09%, p=0.003).

Conclusion: Our results suggest that *BDNF* rs11030104 influences the response to weight loss after IGB treatment and therefore could be added to the growing list of genetic variants that predict greater weight loss response.

Keywords: BDNF, polymorphism, obesity, intragastric balloon, BMI, weight loss

Introduction

The rate of obesity is increasing at an alarming pace, with certain populations exceeding 50%. According to the world health organization, obesity has doubled in adults and quadrupled in adolescents since 1990.[1] This significant increase has resulted in an urgency to develop treatments for the management of obesity.[2] Among these treatments, medical and surgical devices have become widely available through the use of a variety of techniques and procedures.[3] The intragastric balloon (IGB) is an FDA-approved minimally invasive intervention for weight loss that has been widely used.[4] The implantation of the IGB in the stomach for a specified period of time reduces the stomach capacity. This mechanistic approach provides a sensation of satiety leading to the consumption of smaller meals and, in turn, results in weight loss.[5,6]

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A meta-analysis of 40,000 subjects showed that IGB treatment resulted in weight loss between 11% and 15% of total body weight at the 6-month follow-up.[7] In addition, several randomized clinical trials have shown that IGB is an effective treatment option for the management of obesity. In particular, compared with conventional treatments, IGB has been shown to cause significant weight loss in combination with lifestyle modifications.[8,9] Although weight loss is observed among patients undergoing IGB, interindividual variation in weight loss is evident. For instance, a meta-analysis reported that weight loss among IGB patients varied widely, where treatment resulted in no weight loss or extreme weight loss in some patients, reaching up to 87.5 kilograms (kg).[7,10] Heterogeneity in weight loss is broadly attributed to well-established lifestyle factors, such as the level of physical activity and caloric intake.[11]

In addition to lifestyle factors, genetics also contributes to weight loss outcomes after treatment.[12] Genetic variations associated with obesity have been shown to influence weight loss among individuals undergoing bariatric surgery, diet interventions, and intragastric balloon treatments.[13–15] However, the limited number of variants associated with weight loss following interventions highlights the need for further research. Identifying additional weight loss related variants are essential for the construction of genetic risk scores (GRS) that can help predict responders and non-responders to obesity treatments.[16]

The *brain-derived neurotrophic factor (BDNF)* gene has been found to be associated with obesity.[13] The BDNF protein is involved in the growth and survival of neurons in the brain and has been found to play a role in appetite and energy balance regulation. The role of *BDNF* has been well documented in *BDNF* knockout experiments, which demonstrated hyperphagia and obesity development in mice.[17] Additionally, a few single nucleotide polymorphisms (SNPs), such as rs11030104 and rs6256, in the *BDNF* gene have been found to be associated with a greater risk of obesity and have been suggested to influence weight loss following bariatric surgery.[13,18]

The main purpose of IGB is to limit food consumption and thereby induce weight loss. Thus, the study hypothesis is that BDNF, through its appetite control mechanism, could influence the weight loss response after IGB. Identifying genetic factors associated with successful weight loss after IGB interventions may identify responders and non-responders prior to treatment. The aim in this study was to examine the influence of the *BDNF* SNP rs11030104 on weight loss in overweight and obese patients receiving IGB treatment.

Methods

Participants

A total of 106 patients who were overweight or obese and who underwent IGB insertion using an Elipse balloon (Allurion Technologies, Wellesley, MA, USA) or a Bioenterics Intragastric Balloon (BIB) (Inamed Health; Santa Barbara, CA, USA) were enrolled in this cross-sectional study. The analytical sample included data from 71 patients who had baseline and data at the 3-month follow-up measurements. Patients were recruited from "The Clinic", an obesity management centre (Kuwait City, Kuwait) between November 2020 and April 2021. The study was approved by the Ethics Committee of the Ministry of Health in Kuwait (#1261/2020). Subjects under the age of 18 were excluded from the study. Subjects with a body mass index (BMI) above 27.5 kg/m^2 were eligible for the procedure unless they had liver cirrhosis, Crohn's disease, pregnancy, previous gastric surgery, or anticoagulants and were therefore excluded from receiving the IGB intervention. Written informed consent was obtained from the participants prior to enrolment in the study.

Anthropometric Assessment

Weight loss was the primary outcome of interest in this study. Baseline weight (kilograms) and height (meters) were measured using standard protocols prior to IGB insertion. BMI was calculated as kg/m^2 (weight (kg)/height (m^2)). Overweight and obesity were defined according to what is used by the World Health Organization and the National Institute of Health for adults.[19] Anthropometric measurements were recorded at the 3-month (t3) follow-up. Three weight loss metrics were used according to the accepted criteria.[20] These included excess weight loss (%EWL), excess body mass index loss (%EBMIL) and total weight loss (%TWL), all of which were calculated at three months following IGB insertion. Weight loss was calculated using the following formula: %EWL = [(initial weight − current weight)/(initial weight − ideal weight)] × 100, %EBMIL = [(initial BMI − current BMI)/(initial BMI – 24.9)] × 100 and %TWL = [(initial weight − current weight)/(initial weight)] × 100.[18]

DNA Collection, Extraction, and Genotyping

Saliva samples were collected using DNA Genotek Oragene self-collection saliva kits (ORA-600), and genomic DNA was extracted using prepIT. The L2P purification kit was used following the manufacturer's protocol. Genotyping of the *BDNF* polymorphism (rs11030104) was performed using a TaqMan allelic discrimination assay (assay ID: C___1751792_10) from Life Technologies (Thermo Fisher Scientific) according to the manufacturer's protocol. The assay was run on a QuantStudio™ 7 Flex Real-Time PCR system (Applied Biosystems, Foster City, CA, USA).

Statistical Analysis

Patient characteristics and variables were expressed as the mean ± standard deviation (SD) and frequencies (percentages) where appropriate using SPSS version 27.0 (SPSS Inc., Chicago, IL). Associations between the *BDNF* rs11030104 genotype and weight loss metrics were assessed using the "SNPassoc" package from R statistical software.[21] Both additive and dominant genetic models were selected to assess the associations between genotypes and phenotypes. Multiple linear regression, adjusting for the effects of sex and age, was performed, and the results are represented as beta coefficients (B) with 95% confidence intervals (CIs). Moreover, logistic regression was used to determine odds ratios (ORs) and 95% CIs.

Results

A total of 106 patients who were overweight or obese, predominantly women (75.5%), underwent intragastric balloon intervention using either Elipse (78.3%) or BIB (21.7%). A total of 71 participants completed the 3-month follow-up assessment (loss to follow-up: 33%). Patient characteristics are presented in Table 1. The characteristics of the total enrolled participants (n = 106) and the subjects who completed the 3-month follow-up (n = 71) were similar (Table 1).

Table 1 Baseline (t0) and 3-Month (t3) Follow-Up Characteristics of Samples with Genotype Frequencies

Variables	Total Patients (n = 106)	3-Month Follow-Up (n = 71)
Age (yr), mean±SD	30.69 ± 8.37	31.86 ± 7.74
Sex, n (%)	80 (75.5)	54 (74.3)
Female	26 (24.5)	17 (25.7)
Male		
Type 2 Diabetes	7 (6.6%)	5 (7%)
PCOS	18 (22.5%)	12 (22%)
Weight (t0) (kg), mean±SD	95.58 ± 18.16	93.37 ± 17.86
Heights (m), mean±SD	1.64 ± 0.07	1.64 ± 0.08
BMI (t0) (kg/m^2), mean±SD	35.22 ± 4.94	34.50 ± 4.62
Procedure, n (%)		
Elipse	83 (78.3)	58 (81.7)
BIB	23 (21.7)	13 (18.3)
Weight (t3) (kg), mean±SD	–	83.67 ± 15.48
BMI (t3) (kg/m^2), mean±SD	–	30.97 ± 4.17
%TWL (t3), mean±SD	–	10.17 ± 5.75
%EWL (t3), mean±SD	–	41.80 ± 28.63
%EBMIL (t3), mean±SD	–	41.29 ± 29.28
***BDNF* genotypes (n)**		
AA	65 (0.613)	44 (0.62)
AG	31 (0.292)	21 (0.295)
GG	10 (0.095)	6 (0.085)

Abbreviations: SD, standard deviation; BMI, body mass index; PCOS, polycystic ovary syndrome; BIB, bioenteric intragastric balloon; %TWL, percentage of total weight loss; %EWL, percentage of excess weight loss; %EBMIL, percentage of body mass index loss.

Weight Loss Metrics

Three metrics were used to measure weight loss: %TWL, %EWL and %EBMIL. The baseline (t0) was used as a reference time point and was followed up after 3 months (t3) for weight loss calculations. A variation in weight loss was observed, with a recorded maximum %TWL of 23% and a minimum of −7% among participants.

BDNF rs11030104 Genotypes and Relationship with BMI and Weight Loss Metrics

The *BDNF* genotype frequencies are shown in Table 1 and were consistent with the Hardy–Weinberg equilibrium ($P = 0.14$). No association was observed between the genotypes and baseline BMI after controlling for sex or age (p=0.748) (Table 2A). The BMIs of carriers of the homozygous wild-type AA genotype were similar to those of carriers of the homozygous mutant GG genotype (35.4 kg/m^2 and 35.6 kg/m^{2,} respectively).

This study observed a significant association between the *BDNF* polymorphism and weight loss across all assessed metrics (p<0.05) (Table 2A). As shown in Figure 1, subjects with AA genotype experienced greater weight loss across all metrics than those with AG and GG genotypes. An additive genetic model was performed in which carriers of the A-allele showed increased weight loss after controlling for both age and sex. Carriers of the AG and GG genotypes experienced a mean of TWL of 8.74% and 5.09% respectively, whereas carriers of the AA genotype reached a mean of TWL of 11.55% (Table 2A). Moreover, a similar trend was also observed in %EBMIL and %EWL (Table 2A). In addition, a dominant genetic model showed the same association with weight loss across all metrices where carriers of the AA genotype experienced significant weight loss when compared to the other genotypes (Table 2B).

The association between *BDNF* polymorphisms and categorical metrics was also assessed (Table 3). The categorical %TWL was defined as those who achieved TWL equal to or greater than 10% versus those who achieved TWL less than 10%, whereas the categorical %EWL and %EBMIL were defined as those who achieved a loss equal to or greater than 40% versus those who achieved less than 40% (Table 3). This study found that the A allele of the *BDNF* polymorphism in an additive genetic model was associated with higher categorical TWL (≥ %10), whereas the G allele was associated with lower categorical TWL (< %10) (p = 0.025) (Table 3A). Similar findings were observed for both the %EWL and %

Table 2 Relationships Between BDNF Genotypes and Baseline (t0) BMI and Weight Loss Rates After 3 Months (t3) of Follow-Up Following IGB

A) Genetic association analysis using an additive genetic model					
***BDNF* rs11030104**	**AA (n=44)**	**AG (n=21)**	**GG (n=6)**	**β[†] (95% CI)**	***P***
BMI (kg/m^2)	35.40 ± 4.97	34.75 ± 3.49	35.60 ± 8.22	−0.22 (−1.557–1.117)	0.748
%TWL	11.55 ± 4.75	8.74 ± 6.51	5.09 ± 6.57	−3.081 (−5.023–1.140)	0.003
%EBMIL	47.88 ± 25.19	35.13 ± 34.55	14.50 ± 19.12	−15.322 (−25.46–5.187)	0.004
%EWL	48.22 ± 25.12	36.12 ± 32.66	14.53 ± 19.80	−15.120 (−25.09–5.319)	0.004
B) Genetic association analysis using a dominant genetic model					
***BDNF* rs11030104**		**AA (n=44)**	**AG and GG (n=27)**	**β[†] (95% CI)**	***P***
BMI (kg/m^2)		35.40 ±4.97	34.95 ± 4.94	−0.54 (−2.35, 1.117)	0.552
%TWL		11.54 ± 4.75	7.92 ± 6.58	−3.55 (−6.18, −0.91)	0.01
%EBMIL		47.88 ± 25.19	30.54 ± 32.63	−17.55 (−31.28, −3.82)	0.014
%EWL		48.22 ± 25.12	31.32 ± 31.3	−17.12 (−30.09, −3.767)	0.014

Notes: [†]Adjusted for sex and age.
Abbreviations: BMI, body mass index; %TWL, percentage of total weight loss; %EWL, percentage of excess weight loss; %EBMIL, percentage of body mass index loss; *P, P* value; β, beta coefficient; CI, confidence interval.

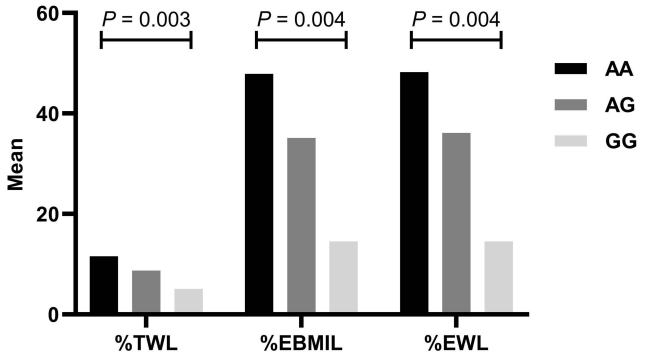

Figure 1 Mean levels of weight loss metrics according to genotypes of *BDNF* gene polymorphism rs11030104. Weight loss metric include, percentage of total weight loss (%TWL), percentage of body mass index loss (%EBMIL), and percentage of excess weight loss (%EWL).

EBMIL categories (p = 0.015) (Table 3A). On the other hand, in a dominant genetic model, carriers of the AA genotype were found to be associated with higher categorical %EWL and %EBMIL, p = 0.048 (Table 3B).

Discussion

Minimally invasive IGB has been proven to be a successful treatment option for weight loss; however, heterogeneity in weight loss response has been observed in recent studies.[10] For the first time, an association between *BDNF* rs11030104 and the extent of weight loss after 3 months of IGB treatment is reported. A-allele carriers were found to be better

Table 3 Relationships between *BDNF* genotypes and categorical weight loss metrics after 3 months of IGB treatment

A) Genetic association analysis using an additive genetic model					
***BDNF* rs11030104**	**AA (n=44)**	**AG (n=21)**	**GG (n=6)**	**OR[†] (95% CI)**	***P***
10 < %TWL (n=32)	16 (36%)	11 (52%)	5 (83%)		
10 ≥ %TWL (n=39)	28 (64%)	10 (48%)	1 (17%)	2.603 (1.127 - 6.013)	0.025
40 < %EBMIL (n=39)	20 (45%)	13 (61%)	6 (100%)		
40 ≥ %EBMIL (n=32)	24 (55%)	8 (39%)	0 (0%)	2.965 (1.234 - 7.123)	0.015
40 < %EWL (n=39)	20 (45%)	13 (61%)	6 (100%)		
40 ≥ %EWL (n=32)	24 (55%)	8 (39%)	0 (0%)	2.965 (1.234 - 7.123)	0.015
B) Genetic association analysis using a dominant genetic model					
***BDNF* rs11030104**		**AA (n=44)**	**AG and GG (n=27)**	**OR[†] (95% CI)**	***P***
10 < %TWL (n=32)		16 (36%)	16 (59%)		
10 ≥ %TWL (n=39)		28 (64%)	11 (41%)	2.613 (0.927 - 7.362)	0.069
40 < %EBMIL (n=39)		20 (45%)	19 (70%)		
40 ≥ %EBMIL (n=32)		24 (55%)	8 (30%)	2.831 (1.009 - 7.945)	0.048
40 < %EWL (n=39)		20 (45%)	19 (70%)		
40 ≥ %EWL (n=32)		24 (55%)	8 (30%)	2.831 (1.009 - 7.945)	0.048

Notes: [†]Adjusted for sex and age.
Abbreviations: BMI, body mass index; %TWL, percentage of total weight loss; %EWL, percentage of excess weight loss; %EBMIL, percentage of body mass index loss; *P*, *P* value; OR, odds ratio; CI, confidence interval.

responders than G-allele carriers after IGB treatment, with the A-allele being associated with greater %EWL, %EBMIL, and %TWL in an additive genetic model as well as in a dominant genetic model. The A-allele was also able to differentiate between those who achieved low weight loss and those who achieved high weight loss when categorizing the metrices used.

The current studied intronic polymorphism (rs11030104) has been reported to be in linkage disequilibrium (r^2>0.8) with the extensively studied nonsynonymous *BDNF* Val66Met polymorphism (rs6265) and has been used as a proxy SNP for one another.[22] Functional studies have shown that the SNP rs6265 impacts gene expression in a dose-dependent manner, where both heterozygosity and homozygosity for the minor Met allele were found to be associated with decreased *BDNF* activity.[23,24] This finding suggests that our A allele of rs11030104 may be linked to the highly active Val allele of rs6265. *BDNF* knockout has been shown to cause hyperphagia and obesity and exogenous administration of BDNF restores food intake and promotes weight loss in obese mouse models.[25–28]

Several publications on *BDNF* variations have shown contradictory and/or inconsistent results, with opposite alleles being associated with obesity that are dependent on sex, nutrition and smoking status.[29–32] A study by Ma et al revealed that the association of the *BDNF* variant rs6265 with obesity was sex dependent and that this variant interacted with polyunsaturated fatty acids.[30] The study revealed that the G allele was associated with obesity in men, whereas the A allele was associated with obesity in women. In addition, Yang et al reported that the A-allele of rs11030104 was associated with obesity in heavily smokers, whereas no association was found in nonsmokers. The authors suggested that smoking might modulate the association with obesity via epigenetic modifications.[29]

The current study did not observe an association with obesity, which could have been due to the lack of a control cohort with a normal BMI for comparison. In a meta-GWAS, the A-allele of rs11030104 was found to be associated with higher BMI and was among the top polymorphisms associated with obesity.[13] In addition, a study by Monnereau et al revealed rs11030104 to be associated with satiety responsiveness; however, no association was observed with obesity.[33] Such inconsistency warrants further investigation on the mechanistic role such alleles have on BDNF activity.

The A-allele was clearly found to be associated with greater weight loss in all metrices, and the authors believe this finding could be explained by the pathophysiological changes arising from the insertion of the IGB, which could have modulated this association with BDNF. IGB occupies approximately one-third of the stomach cavity and therefore reduces the capacity of the stomach to accommodate food, resulting in reduced caloric intake.[34] Kishi et al reported that calorie restriction in rats upregulates BDNF through an antioxidant effect.[35] Our only rational explanation is that carriers of the G-allele, which is in LD with the functional variant rs6265 Met-allele (low activity) at position 66 of the BDNF protein, are likely to exhibit impaired BDNF secretion compared with carriers of the high activity Val-allele of rs6265 (The A-allele).[36] This may impact satiety responsiveness, as carriers of the G-allele may not feel full and eventually consuming more calories, leading to poor weight loss compared with that of carriers of the A-allele.[33] However, this hypothesis could not be tested in our study due to the lack of BDNF activity measurements and dietary intakes.

In light of the current findings, this study has limitations, as the absence of BDNF activity and dietary intake measures prevented us from assessing the molecular effect of the variant or any gene–environment interactions. Although a strong association between our variant and all weight loss metrics, our 33% loss to follow-up is a limitation, and future work is needed to replicate our findings in a larger cohort. It is therefore necessary to confirm our findings and assess the mechanism and functional role of BDNF in weight loss after surgical interventions.

Conclusion

In conclusion, for the first time, this study has reported the influence of the *BDNF* rs11030104 variant on weight loss after IGB treatment in a cohort of overweight and obese individuals. The findings are consistent with previous work on the role of *BDNF* in influencing weight loss. In addition, such findings can be added to the growing list of variants that can help predict and identify responders to weight loss prior to medical and surgical intervention.

Data Sharing Statement

All the data generated or analysed during this study are included in this article. Further enquiries can be directed to the corresponding author.

Statement of Ethics

We certify that the work conducted in this research complies with the ethical standards recommended by the Helsinki Declaration and that the work has formally been approved by the Ethical Committee of the Ministry of Health in Kuwait (#1261/2020). Written informed consent was obtained from the participants prior to enrolment in the study.

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Disclosure

The authors have no conflicts of interest to declare.

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