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Weight Changes in STN versus GPi DBS: Results from the COMPARE Parkinson's Disease DBS Cohort

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Abstract

Background—Parkinson's patients, on average, gain weight following DBS.

Objective—To determine potential differences in weight gain when comparing the STN versus the GPi target.

Methods—A retrospective analysis was performed on the prospective randomized cohort of NIH COMPARE DBS patients who received unilateral STN or GPi DBS. Baseline weights were recorded prior to DBS surgery and at 6, 12, and 18 months post-operatively. Relationships between weight change and changes in BDI score, UPDRS motor score (part III) (also the dyskinesia duration and disability subscores from UPDRS IV), and HY stage were determined via Spearman's rank order correlation coefficients. Regression analyses were performed to investigate the effects of potential factors on weight change over time.

Results—Patients in the COMPARE DBS cohort gained a significant amount of weight—a mean of 4.86 lbs (SD 8.73) (p-value = 0.0006), but there was no significant difference between STN and GPi targets (weight gain of 4.29± 6.79 and 5.38±10.32 pounds, respectively; p-value = 0.684). Weight gain did not correlate with BDI score change, UPDRS motor score, dyskinesia duration, dyskinesia disability change, or the HY stage (p-values were 0.617, 0.210, and 0.305 respectively). No specific variable was associated with weight gain, and there were no differences in binge eating post-surgery in either target.

Conclusion—There were significant changes in weight over time following DBS therapy. However, neither BDI score change nor UPDRS score change or dyskinesia was correlated with weight gain. No significant factor was associated with the weight change.

Keywords

Deep brain stimulation; hypothalamus; diet; outcome; binge

Introduction

Patients with advanced Parkinson's disease (PD) have been increasingly implanted with deep brain stimulation (DBS) devices to better control both motor symptoms and fluctuations.¹ Approved FDA approaches to DBS include placing a lead(s) in either the globus pallidus internus (GPi) or the subthalamic nucleus (STN). Despite promising motor outcomes, a noticeable weight gain has been observed post-DBS surgery in many of the implanted patients.^{2, 3} There are open and debated questions about DBS related weight change including target specificity, underlying cause, and mechanism of action. Additionally, there has been worry that post-operative weight gain may detract from the overall benefits of surgery and/or induce metabolic disorders⁴. Most available studies on weight gain have focused on bilateral STN stimulation and there has been little data on GPi. In the COMPARE PD DBS cohort, patients were randomized to receive unilateral STN or alternately GPi DBS. Cognitive, motor, and quality of life outcomes from this cohort were recently reported.^{5, 6} Prior to randomization, it was hypothesized that there would be significant weight gain following DBS surgery, and that STN DBS would be a bigger offender. We further hypothesized that weight gain would be due to spread of current into the hypothalamic associated circuits, and that post-DBS changes would involve behaviors such as binge eating and carbohydrate craving.

Methods

Fifty-two patients were randomized to receive either unilateral STN or unilateral GPi DBS in the parent study. Forty-four of these patients possessed a complete dataset that included weight values (pre-and post-operatively at specific intervals) as well as other outcome measures. IRB approval was obtained for the study, and all patients signed informed consents. Baseline weights in pounds were recorded prior to the first DBS surgery and at 6, 12, and 18 months post-operatively. The weight measurement for comparison between targets was conducted at 6 months post-DBS when all patients had a unilateral lead. Weight measurements were also collected at 12 and 18 months. Following 6 months post-DBS, select patients received a second (bilateral lead). A mixed effect model was used to determine the trend in weight change between targets with a correction for the discrepancy of unilateral vs. bilateral leads. Other data to explore potential factors that may have affected weight change were collected including: age, gender, unified Parkinson Disease Rating Scale (UPDRS) motor score and dyskinesias duration and disability scores at baseline in the off dopaminergic medication state, the on medication state, and at 4 months post-operatively in the off dopaminergic medication/on DBS state; Hoehn and Yahr off staging score; and the Beck Depression Inventory (at baseline and 6 months).

A Binge Eating Scale (BES) was administered to all available and willing patients but was notably not performed at baseline (at the study onset the authors did not appreciate that binge eating would be an important factor to measure). A BES was collected in all cases following six-month follow-up visits. Based on these results, the total scores were compared for the patients with STN stimulation versus GPi stimulation to determine if there was a weight change and whether there was target specificity in binge eating behavior.

Statistical analysis was performed on the complete data set using SAS (version 9.1). Descriptive statistics were obtained on the clinical variables. Differences between the GPi group and STN group were compared using two-sample t-test for continuous variables and chi-square test for categorical variables. We examined relationships between weight change and changes in the Beck Depression Inventory (BDI) score, the Unified Parkinson Disease Rating Scale (UPDRS) motor score, as well as dyskinesia duration and disability via Spearman's rank order correlation coefficients. Furthermore, a linear regression analysis

was performed to examine the effects of potential factors on weight change between baseline and 6 months post-DBS surgery. In addition, a mixed effects model was applied to investigate the difference between stimulation DBS targets in trend of weight change from baseline to 18 months post-DBS surgery.

Results

Descriptive statistics of the clinical variables (Table 1) showed that average values of BDI change (-3.0 vs. 1.06) and Stigma (39.95 vs. 27.08) were different at a trend level between those patients who received unilateral GPi DBS and those who received STN DBS, while other variables were approximately the same.

There was a significant weight gain of 4.86 pounds (2.2 Kg) ($p = .0006$) at 6 months post-DBS surgery when analyzing the complete COMPARE cohort. However, unlike what was hypothesized, there was no significant difference in weight change between the STN and GPi targets, with weight gain of 4.29 ± 6.79 and 5.38 ± 10.32 pounds, respectively (p -value = 0.684). The range of weight changes was broad for both targets (STN target -7 to 19 pounds; GPi target -14 to 25 pounds). For the patients with GPi stimulation, 16 (70%) gained weight of 10.65 ± 6.98 , 6 (24%) lost weight of 7.77 ± 4.55 , and 1 (4%) remained unchanged. In comparison, 15 (71%) patients who received STN stimulation gained weight of 7.20 ± 5.55 , 4 (19%) patients lost weight of 4.50 ± 2.38 , and 2 (10%) remained unchanged. Once again, there was no significant difference between STN and GPi targets for those patients who did gain weight ($p = 0.141$). There was no difference in post-operative BES scores when comparing between targets (28.07 at STN versus 24.8 at GPi with p -value 0.323). Further, within our cohort, 23 post-DBS patients answered subjective questions on eating behavior. Of these patients, 14 reported carbohydrate cravings (60.9%) and 9 reported no cravings (39.1%). There was no target specificity in carbohydrate cravings (7 were from STN DBS and 7 were from GPi DBS groups, respectively).

Weight gain did not correlate with BDI score change, UPDRS motor score/dyskinesias duration and disability changes, or the HY stage (p -values were 0.617 , 0.210 , 0.188 , 0.794 , and 0.305 , respectively). In addition, we did not find any variables that were significantly associated with weight change between baseline and 6 months post-DBS surgery. Furthermore, time from the first DBS was found to be the only variable that was significantly associated with the weight change (p -value = 0.002) according to the mixed effects model analysis, which used the recorded weights from 6, 12, and 18 months post-DBS surgery. The results showed that the longer the time from surgery, the more weight gain occurred in patients (Figure 1).

Discussion

When carefully examining the 44 patients who were studied utilizing available data from the COMPARE cohort, 31 patients (70%) gained weight by the 6-month follow-up, 10 patients (23%) had weight loss, and 3 patients (7%) remained unchanged. Although there was an overall weight gain within both groups (4.86 lbs), the change was not target specific, as we had hypothesized. Results from this study can be used in preoperative counseling for patients considering STN vs. GPi DBS. Approximately 70% of patients who undergo DBS can expect an average weight gain of 10.65 ± 6.98 with GPi target stimulation compared to 7.20 ± 5.55 with the STN target.

The results also did not reveal a significant difference in the BES or eating behavior between the groups. Further, time from the first DBS was found to be the only variable that was significantly associated with the weight change (p -value = 0.002). These data should help us

to begin to evolve our understanding of the mechanisms underpinning DBS related weight change and its clinical implications.

PD as a neurodegenerative phenomenon has been strongly associated with weight loss, with some experts believing the issue to be related to Lewy Body deposition in non-motor basal ganglia circuitry as well as potential involvement of hypothalamic related circuits.^{7,8,9} Proposed mechanisms for weight loss in PD have included increased energy expenditure, early satiety due to decreased gastrointestinal motility, olfactory impairment, bulbar dysfunction, and a decreased dopaminergic stimulation of the central reward system.¹⁰ Although weight loss has been associated with PD, it is weight gain that has been associated with DBS in the PD population.² It is unknown whether this weight gain will prove beneficial or protective within this population.

Although increases in weight following DBS surgery may be undesirable, they have not been specifically linked to an increased risk of cardiovascular events, diabetes, or other health risks.¹¹ Weight gain following DBS surgery might in fact be a protective factor against adverse events such as a greater susceptibility to falls/fractures, poor nutritional status, or nursing home placement, which often accompany weight loss in the PD population.¹¹ Further, it is plausible that weight gain might be beneficial in men, who tend to gain fat-free mass, while potentially deleterious in women who gain primarily fat mass.⁴ On the other hand, the underlying mechanism for this gender difference is still to be explained.

Similar to PD, Huntington's disease (HD) is a neurodegenerative disease associated with weight loss in affected patients and this is perhaps due to hypermetabolism.¹² Oral nutritional supplements have been suggested for HD patients and the gaining of weight in this population is thought to be helpful to improve longevity.¹³ Whether weight gain proves to be beneficial or deleterious, a recent study has shown that nutritional intervention immediately following DBS surgery may be useful in controlling weight change.¹⁴ In comparing a group of PD patients who received nutritional intervention immediately after surgery (1 week) to a group who received delayed intervention (2.5 $\pm$ 1.6 years), the early intervention group did not gain a significant amount of weight.

A review of the available literature regarding DBS and the associated weight changes (usually gain) reveals that most studies included only the STN target, and all studies uniformly reported weight gain (see Table 2). In some studies, the experimental group of patients (STN-DBS) was compared to a control PD group without DBS. The STN-DBS patients in these investigations experienced gain while non-DBS PD patients lost weight. The time frames for each of the studies varied but the weight gain was approximately 3 kg (6.6 lbs) at 3 months and 9 kg (19.8 lbs) at 1 year (in bilateral STB-DBS cases). According to these published experiences, for unilateral STN-DBS the approximate weight gain was 3.4 $\pm$ 3.0 kg at 6 months (7.5 $\pm$ 6.6 lbs), and we observed less weight gain in the unilateral groups included in our study. The findings from these many studies have suggested that the weight gain may have been due to decreased energy expenditure that was in part due to reduced dyskinesia, and in part due to a reduction in dopaminergic therapy.

Reduced overall energy expenditure directly resulting from DBS related dyskinesia reduction has been posited as a leading explanation for weight gain.^{1,15,4} In our study, both STN and GPi patients improved in dyskinesia, and although one target was not statistically better, this overall improvement may have contributed to weight gain. Montaurier observed that energy metabolism was decreased post-DBS surgery while energy intake was unchanged.⁴ The relationship of energy metabolism to dyskinesia and dyskinesia reduction remains unknown. In future studies, more careful correlation of dyskinesia score (with

dyskinesia diaries which were not done as part of COMPARE) and weight gain will need to be documented. Most authors do not believe, however, that dyskinesia reduction in itself is responsible for the weight gain. One interesting finding that was not unique to this study was that approximately 20% of patients with DBS lost weight. One wonders if a comparison of the groups (gainers vs. losers) may indicate a potential underlying mechanism.

Several potential mechanisms have been proposed as explanations for the weight gain following DBS surgery. In one case report involving STN DBS, a single patient had a remarkable improvement in PD symptoms, gained 10 kg (22 lbs), and developed an increased craving for sweets¹⁶. Our own observations have revealed several cases similar to this report, and we wondered whether carbohydrate craving could be more common post-DBS than previously recognized. Additionally, a recent study showed that there was a significant difference in BMI change between STN and GPi bilateral DBS surgery. At 6 months post bilateral DBS surgery, BMI had increased by an average of 8.4% in the STN group and only 3.2% in the GPi group ($p < 0.048$). Perhaps the placement of the second electrode may prove a significant contributor to weight gain in this population of patients.³ Much skepticism, however, remains in these studies and in their interpretation. One leading thought is that spread of current to the hypothalamic satiety centers may play a larger role than previously appreciated.

A regional or circuit effect of STN DBS on the hypothalamic satiety center may therefore be hypothesized as one potential contributing cause for weight gain.⁴ Weight gain has been reported in multiple targets following PD surgical therapy, including unilateral pallidotomy, bilateral pallidal DBS, and bilateral STN DBS.¹ A strong piece of evidence against an exclusive current spread mechanism is that weight gain has been observed following GPi ablation.¹⁷ Our data, which showed no difference in BES scores or carbohydrate cravings between targets, argues against an exclusive and simple regional/circuit spread of stimulation hypothesis, unless the DBS is affecting the same circuit both up and downstream (i.e. connectivity in STN and GPi).

Results from recent GDNF studies revealed that GDNF-mediated activation of various hypothalamic areas was important in observed weight loss.¹⁸ There are resident hypothalamic DA neurons, the nigrostriatal DA tract (known to be involved in feeding and weight loss) passing through the lateral hypothalamus, and through the medial forebrain bundle (MFB). It is plausible that DBS neuromodulates and stimulates the same or similar circuitry. DBS, unlike GDNF in the MFB, may have affected fibers of passage in the nigrostriatal pathway, which may have induced weight gain instead of loss in the majority of cases. Alternatively, the 20% of patients who lost weight post-DBS might have invoked similar circuitry as to that seen in GDNF.

There are several limitations associated with this study. The cohort consisted of a small sample size of only 44 patients. Additionally, the Binge Eating Scale was only administered following implantation of the DBS and there was no baseline analysis of bingeing and carbohydrate craving. Further, the regression analysis, which utilized the 6, 12, and 18-month weights post-DBS surgery, included both bilateral and unilateral DBS patients. Despite these limitations however, we feel that the prospective randomized nature of the study has provided important insights, particularly in weight gain in more than just the STN target. Additionally, the data that revealed depressive symptoms (i.e. the BDI) was not related to weight gain further eliminates another potential factor.

Future studies should include more information on activity (i.e. exercise) levels prior to and following surgery. Further, the Binge Eating Scale and a food diary (i.e. carbohydrate

intake) should be administered at baseline and at 6 months following DBS in order to more effectively draw conclusions.

Although DBS has great benefits for motor symptoms and fluctuations, patients should be aware there is associated weight gain in either STN or GPi DBS. Future studies will need to focus more closely on potential underlying mechanisms, and there will need to be focused pre-operative education plans for patients.

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Figure 1.
Weight at baseline, 6-, 12-and 18-months post-DBS surgery by stimulation targets*
*The I bars indicate standard error.

Table 1

Descriptive Statistics comparing patients who received GPi vs. STN DBS [Mean (SD) or N (%)]

Variable	All	GPi (N=23)	STN (N=21)	P-Value
Laterality Bilateral	25 (56.8%)	10 (43.5%)	15 (71.4%)	0.062
Unilateral	19 (43.2%)	13 (56.5%)	6 (28.6%)	
Weight change at 6 months follow-up	4.86 (8.73)	5.38 (10.32)	4.29 (6.79)	0.684
BDI score change	-1.18 (6.81)	-3 (5.34)	1.06 (7.86)	0.067
UPDRS III change	-11.48 (13.59)	-12.05 (16.42)	-10.84 (9.98)	0.783
Height	56.99 (4.05)	57.29 (4.11)	56.6 (4.07)	0.629
BES	26.38 (8.74)	24.8 (6.7)	28.07 (10.5)	0.323
Mobility	45.63 (24.33)	43.59 (22.84)	47.86 (26.25)	0.567
ADL	38.73 (20.06)	36.23 (17.74)	41.47 (22.46)	0.394
Emotional	32.67 (20.57)	30.43 (19.03)	35.12 (22.34)	0.457
Stigma	33.81 (22.81)	39.95 (22.67)	27.08 (21.5)	0.061
Social	19.51 (20.72)	23.19 (23.02)	15.48 (17.54)	0.222
Cognitions	30.54 (21.41)	30.71 (22.68)	30.36 (20.47)	0.958
Communication	33.52 (22.19)	33.33 (22.61)	33.73 (22.28)	0.954
Discomfort	43.37 (25.2)	42.03 (25.19)	44.84 (25.75)	0.716
Baseline UPDRS III	42.43 (11.91)	39.83 (9.48)	45.29 (13.77)	0.130
Baseline BDI score	8.8 (6.54)	9.43 (7.28)	8.1 (5.72)	0.504
HY Stage	2.94 (0.65)	2.8 (0.67)	3.11 (0.61)	0.132
Dyskinesias duration	-0.57 (1.14)	-0.83 (1.1)	-0.32 (1.16)	0.172
Dyskinesias disability	-1.05 (1.09)	-1.16 (1.21)	-0.95 (0.97)	0.559

Table 2

Review of the Relevant Literature of DBS and Weight Change

Author	DBS Target Site	Number of Patients in Study	Results	Notes
Walker, H. C. 11	STN	39 (27 men, 12 women)	Weight gain	Unilateral STN- DBS patients gained 3.4 ± 3.0 kg at 6 months
Montaurier, C. 4	STN	23 (16 men, 7 women)	Weight gain	Bilateral STN patients gained an average 3 kg at 3 months post-surgery; quality of weight gain was gender-specific
Macia, F. 15	STN	19 (11 men, 8 women)	Weight gain	Bilateral STN patients had a significant weight gain(WG, $+9.7 \pm 7$ kg)
Barichella, M. 1	STN	30 (22 men, 8 women)	Weight gain	Bilateral STN patients gained an average of 9.3 ± 6.2 kg in 1 year.
Bannier, S. 19	STN	22 (15 men, 7 women)	Weight gain	Bilateral STN patients showed an average weight gain of 3.1 kg in 3 months.