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Weight changes following deep brain stimulation surgery for Parkinson's disease: A systematic review.

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Abstract

When Parkinson's disease (PD) symptoms are no longer effectively managed by medication, deep brain stimulation (DBS) can be an effective surgical method of managing symptoms. The surgery involves implanting electrodes in targeted brain nuclei and administering a high frequency electrical stimulation. Excessive weight gain is a commonly reported side effect of the surgery. The current publication aims to systematically review the available literature to determine the extent of weight gain following DBS surgery of the subthalamic nucleus (STN), globus pallidus internus (GPi), ventral intermediate nucleus of the thalamus (VIM) or pedunculopontine nucleus (PPN) in patients with PD including the frequency, amount and time period of weight gain as well as the differences between DBS targets. Forty studies were identified through a systematic search with 14 reporting only the frequency of patients experiencing weight changes and 26 reporting post-operative changes in weight, BMI and/or body composition. All of the studies reported weight gain following surgery with between 62 and 100% of participants affected regardless of surgical target and at intervals from 1 to 31 months post-operatively. Reported weight gain is greater in STN-DBS, which is more commonly used as a target, than GPi-DBS. Fat mass increases in both genders and may result in increased central adiposity and risk of chronic disease. Results of the studies indicate that weight may begin to decrease between 18 and 24 months following surgery. The mechanisms of weight gain are not well understood. Future research should focus on documenting the weight trajectory in PD, pre and post-operatively. An individualized nutrition intervention has been shown to be successful in managing weight post-operatively, and long-term monitoring of weight and nutritional status may be necessary to prevent excessive weight changes.

Introduction

Parkinson's disease (PD) is one of the most common neurodegenerative diseases[1] affecting adults of any age, but it particularly affects those over the age of 65 years.[2] It is a progressive disease with individual variations in the rate of progression and presence of symptoms.[3] These symptoms include motor symptoms of bradykinesia, akinesia, rigidity and tremor[1] as well as non-motor symptoms (cognitive impairment, neuropsychiatric symptoms, sleep disorders, autonomic symptoms, gastrointestinal dysfunction).[4]

The first line of symptom management is the use of dopaminergic medications, including the use of levodopa to restore dopamine levels.[5] Long-term use of levodopa, with the accompanying dose increases, can result in motor symptom fluctuations, or "off" times with sub-optimal symptoms management, and dyskinesias (excessive involuntary movements), both of which increase in frequency and severity with time.[6]

In this issue:

Weight changes following deep brain stimulation surgery for Parkinson's disease: A systematic review.
1-14

Attending 2013 FNCE®?
14

Research DPG CPE Article Questions
15

The Chair's Message
16

Hot Topics in Food Science and Health: Raw Broccoli versus Cooked Broccoli
17-18

Notes from the Secretary's Desk
19

Letter from the Editor
19

Treasurer 's Report
20

Member Spotlight
21-22

Upcoming Conferences
23

Research DPG CPE Article Answers
23

Certificate of Attendance
24

Research DPG Elected Officials 2013-2014
25

RDPG List of Official Volunteers
26

When the PD symptoms are no longer effectively managed by medication, deep brain stimulation (DBS) can be an effective surgical method of managing symptoms.[6]

DBS is a modifiable and reversible stereotactic surgery and is currently considered the gold standard for the surgical treatment of PD.[7] The surgery involves implanting electrodes either unilaterally or bilaterally in the brain and providing high frequency electrical stimulation to the target nuclei.[7] The current targets for PD include the subthalamic nucleus (STN), the globus pallidus internus (GPi), the ventral intermediate nucleus of the thalamus (VIM) and, more recently, the pedunculopontine nucleus (PPN). The choice of target depends on the predominant symptoms and other comorbidities. STN-DBS provides benefits for a number of PD symptoms and is the most common surgical target.[8] Following DBS surgery, medication doses can often be decreased or eliminated altogether.[6]

Guidelines for DBS list weight gain as a potential adverse event, particularly with STN-DBS.[6,8–10] It has been suggested that this weight gain may increase the risk of cardiovascular disease, diabetes and dementia following surgery.[11,12] A narrative review has been published describing this phenomenon and the potential causes,[12] but the extent of the problem is not yet well understood.

The aims of this publication are to systematically review the literature to determine the extent of weight gain following DBS surgery of the STN, GPi, VIM or PPN in patients with PD including the frequency, amount and time period of weight gain as well as the differences between DBS targets.

Methods

Study characteristics

Clinical trials of DBS surgery in Parkinson's disease with longitudinal monitoring of post-operative outcomes were included. Participants of any age with a diagnosis of Parkinson's disease (as defined by the authors of the studies) who had undergone unilateral or bilateral DBS of the STN, GPi, VIM or the PPN and who did not receive a structured nutrition intervention following the surgery were considered. Studies reporting the results of surgery introducing lesions in the brain were excluded. Studies were included if they reported changes in body weight (pounds or kilograms) from pre-operative values to any time point following DBS surgery. Differences in follow-up times between studies are reported. Studies were also included if the frequency of weight changes was reported without reporting of the specific weight changes.

Report characteristics

Publications were included if they presented new and original results relating to weight changes following DBS surgery. Therefore, protocols, conference abstracts where the data was also available in a full-length publication and existing review/commentary papers were excluded. Publications were limited to the English language within the full year range available for each database.

Search methods

Searches were undertaken for all available years in the CINAHL (Cumulative Index to Nursing and Allied Health Literature), Medline, PsycInfo, ScienceDirect, WorldCat and OpenGrey databases as well as the entire Cochrane library. The following search phrase was used: Parkinson* AND ("deep brain stimulation" OR (nucleus AND stimulation)) AND weight. The last search was conducted on December 25, 2012. Reference lists of existing review articles were reviewed for additional publications. The resulting flow of studies through the review process is shown in Figure 1. Review of authors and sample size/characteristics was conducted to identify duplicate publications that were then removed. Eligibility assessment was conducted in an un-blinded manner by the author. Studies were excluded firstly by titles, followed by abstracts and lastly by a full-text review. Letters to the editor were excluded.

Data collection

The author used a custom data extraction sheet to extract the data including a) participant characteristics (gender, age, PD duration and severity), b) surgical target, c) weight measurement methods and frequency, d) weight changes, e) length of follow-up, f) loss to follow-up, and g) whether any other anthropometric measures were collected (fat free mass or fat mass). Where gender differences were reported, the results were included.

To highlight the risk of bias in the studies, the number of participants lost to follow-up was documented as well as any specific exclusion criteria that would have influenced the results. The method of obtaining the weight changes was documented. The aim of the current study is not

Figure 1

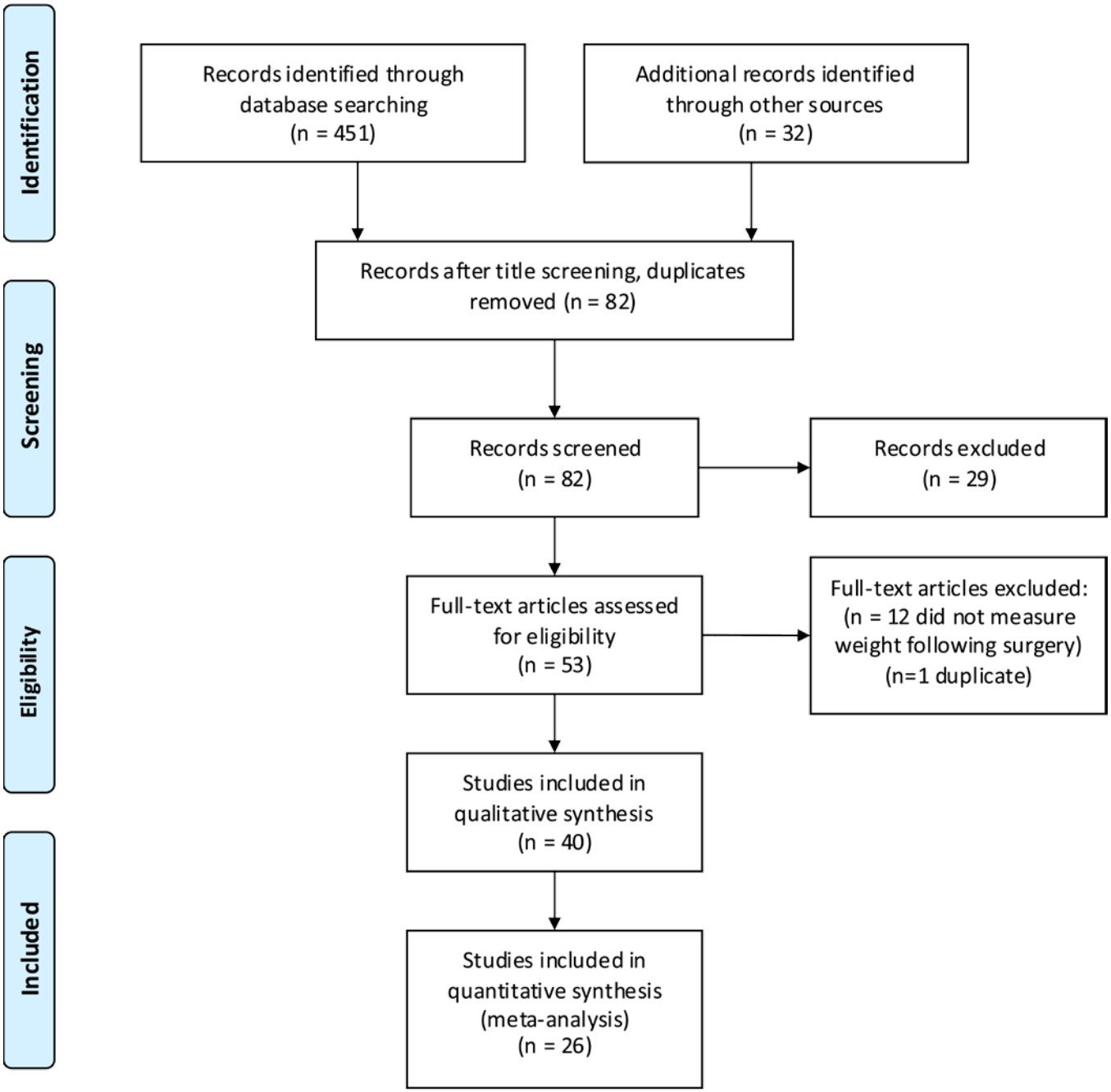

Figure 1: Search methods to retrieve articles reporting weight gain following deep brain stimulation (DBS) surgery in Parkinson's disease (PD)

to evaluate the surgical intervention but the frequency and extent of weight changes following surgery. Therefore, the bias associated with the selection of patients for the surgery is not evaluated.

Statistical analysis

The summary measures for weight or BMI changes reported in each of the studies were used. Individual data was provided in the studies by Romito (2002)[13] and Růžička (2012)[14] which was used to calculate the mean±s.d weight change and the percentage weight change for the entire sample. Due to the variation in the frequency and timing of the pre-operative and post-operative measurements, the data was not pooled for meta-analysis purposes.

Results

Search results

The study selection resulted in a total of 40 studies from which data were extracted (**Figure 1**). Of the 82 abstracts screened from the original selection of 483, two abstracts were excluded because the full text records were not available in English, and the full text was not available for four studies resulting in 53 full-text articles, which were assessed for eligibility. Fourteen of the 40 studies included for analysis reported weight only as an adverse event without any statistical analyses and are reported separately from the remaining 26 studies.

Characteristics of the studies

Characteristics and results of the 26 studies are included in Table 1. The criteria to determine which patients were eligible for the surgery were similar for all studies and based on guidelines for selection of appropriate patients for DBS.[6,8] These are not included in Table 1; instead, only the criteria used to determine if the participants would be included in the weight change results are listed.

The purpose of 16 of the publications was to report the presence or amount of post-DBS weight change and/or potential contributors to weight gain.[14–30] The remainder reported weight as a secondary outcome with primary outcomes including the long-term efficacy of the surgery,[13,31–33] efficacy of the surgery with a specific technique,[34] change in medication,[35] factors contributing to osteoarthritic pain post-operatively,[36] gastric emptying rate,[37] and the effect of DBS on incentive salience attribution.[38] Collectively, these studies represent a sample size of 792 patients with PD. An additional 14 studies reported weight change as an adverse event following surgery and provided the frequency of occurrence without further details of the weight change (Table 2).[39–52]

Surgical targets

The effect of bilateral GPi-DBS was reported in two studies,[16,49] and the results were compared to the effect of STN-DBS on weight. The effect of bilateral VIM-DBS was reported in only one study,[18] and the remainder included either unilateral[15,17] or bilateral[13,14,16–52] STN-DBS. Lee et al (2011)[17] included 43 people with PD who underwent unilateral STN-DBS where 25 of them were eligible for staged bilateral stimulation within the 2 years following the unilateral placement. The two groups (unilateral (n=18) and bilateral (n=25)) were treated as separate groups for comparison of post-operative weight changes.

Length of follow-up

Pre-operative measurements ranged in time from 12 months prior to surgery to the day of surgery (Table 1). Post-operative measurements ranged in time from 3 months to 48 months (n=26) (Table 1). Many of these studies reported collecting data at more frequent intervals than those for which data was reported. The studies reporting weight as an adverse event (n=14) ranged from 0.5 year to 5 years post-operatively (**Table 2**).

Exclusion criteria and loss-to-follow-up

The exclusion criteria were related to the aims of the studies (Table 1). This included bilateral[15] or unilateral[27] electrode placement as well as the presence of other conditions which could affect weight[19,24,26] and/or gastrointestinal function.[37] The retrospective studies that excluded those without adequate data in the charts did not report the reasons.[15,17,27] Lack of follow-up occurred primarily due to complications of surgery, including inflammation, infection or bleeding.[18,20,21,25] Other reasons were that the participant was deceased[20,33] or refused to participate post-operatively.[20,21,33]

Weight measurement

Fourteen studies reported that weight was measured in the clinic at the time of surgery and in the follow-up visits.[14,16,19–24,26,28,30,32,34,38] Five studies reported weight changes from a retrospective chart review[15,17,18,27] or by asking the participants for weight changes retrospectively.[25] For the remainder, the method of obtaining weight is not known.[13,29,31,33,35–37]

Table 1: Characteristics and results of 26 studies reporting weight and/or BMI changes following deep brain stimulation (DBS) surgery for Parkinson's disease

First author (year)	Participants	Exclusions/Lost to follow-up frequency	Measurement changes (kg)	Weight and/or weight changes (kg/m^2)	BMI and/or BMI
Bilateral GPi-DBS					
Sauleau (2009)[16]	n=14 (10 M, 4 F) Age 58.2±7.0 yr PDD 11.1±4.1 yr	None	Day of surgery 3 mo post- 6 mo post-	 +1.7±6.2 9 (64.3%) increased, 5 (35.7%) decreased	22.9±1.1 23.3±0.9 23.4±0.9 p=.384 (main effect)
Unilateral STN-DBS					
Walker (2009)[15]	n=39 (27 M, 12 F) Age 59.1±10.1 yr PDD 11.4±6.1 yr	Staged bilateral STN-DBS n=8 incomplete 12 mo weight data	12 months pre- Day of surgery 3 mo post- 6 mo post- 12 mo post-	-0.8±2.8 +1.9±6.6, ns +3.4±3.0, ns +4.3±3.2, p<.001 23 (59%) decreased prior to surgery	 +0.4±2.0
Lee (2011)[17]	n=18 (13 M, 5 F) Age 60 ± 2.5 yr PDD 10.3 ± 0.92 yr	n=9 incomplete weight data	Day of surgery 3 mo post- 6 mo post- 12 mo post- 24 mo post-	 +3.9±2.0, p<.001	n/a
Bilateral STN-DBS					
Moro (1999)[35]	n=7 (1 M, 6 F) Age 57.4 ± 5.5 yr PDD 15.4 ± 7.6 yr	None	Day of surgery 16.3±7.6 mo post-	56.1±5.8 64.0±6.0 (+12.8%) 7 (100%) increased	n/a
Romito (2002)[13]	n=22 (11 M, 11 F) Age 56.3 ± 7.7 yr PDD 14.4 ± 5.9 yr	Less than 1 year follow-up n=1 at 13 mo due to bowel adenocarcinoma	Day of surgery 23.1±12.1 mo post-	 +6.7±8.6 (+11.9%), p<.001 19 (86.4%) increased, 3 (13.6%) decreased	n/a
Barichella (2003)[29]	n=30 (22 M, 8 F) Age 60.0 ± 7.1 yr PDD 13.5 ± 3.7 yr	None	Day of surgery 3 mo post- 12 mo post-	 +9.3±6.2 (+14.8±9.8%)	21.6±3.0 24.7±3.7
Romito (2003)[31]	n=33 (19 M, 14 F) Age 58.8 yr PDD 12.8 yr	Prior brain surgery	 Day of surgery 25.7±13.5 mo post-	29 (96.7%) increased 56.6±15.0 73.9±15.9, p<.001 (+11.1%)	 n/a
Ford (2004)[32]	n=30 (19 M, 11 F) Age 56.8 ± 7.1 yr PDD 13.8 ± 5.5 yr	n=2 lived too far away to return	One week pre- 12 mo post-	 +2.8, p=.028	n/a
Macia (2004)[28]	n=19 (11 M, 8 F) Age 59.9 ± 6.6 yr PDD 15.0 ± 3.2 yr	None	Day of surgery 12.7±7.8 mo post-	 +9.7±7.0, p<.0001 18 (62.0%) increased	20.6±3.5 25.3±4.3, p<.0001
Tuite (2005)[27 b]	n=27 (17 M, 10 F) Age 64 yr	Incomplete weight data Unilateral DBS	6 mo pre- Day of surgery 1.5 mo post- 6 mo post-	-1.5lb (-0.7kg)[c], p=.0163 +10lb (+4.5kg) c, p=.001 22 (81.5%) increased, 5 (18.5%) decreased	27.3±1.4 26.6±1.4, p<.02 26.8±1.4, ns 28.0±1.3, p<.02
Østergaard (2006)[33]	n=22 (17 M, 5 F) Age 63.0 ± 8.0 yr PDD 19.0 ± 5.0 yr	n=2 at 12 mo (incomplete weight data); n=4 at 48 mo (2 deceased, 1 unable to travel, 1 refused)	Day of surgery 12 mo post- 48±2 mo post-	73.6±19.3 79.3±18.7 78.5±17.9	n/a
Montaurier (2007)[26]	n=24 (17 M, 7 F) Age 61.1 ± 1.4 yr PDD (M) 9.9 ± 0.6 yr (F) 10.1 ± 1.5 yr	Depression, diabetes, thyroid disease, psychosis, pre-menopausal	1 mo pre- 3 mo post-	 M: +3.4±0.6, p<.0001 F: +2.6±0.8, p<.05	25.2±0.7 26.3±0.7, p<.0001

Chart continues on page 6.

Table 1: continued from page 5.

Novakova (2007)[25]	n=23 (16 M, 9 F) Age 55 (42-65) yr PDD 14 (9-21) yr	n=2 (1 inaccurate retrospective info, 1 inflammation at surgical site)	Unknown time pre- 19 (1-45) mo post- 31 (13-57) mo post-	 +9.4 (range 1 - 25), p<.001 +8.0 (range -4 – 24), p<.001 -1.4 (range -6 – 11) between 19 and 31 mo 6 (26.1%) increased, 14 (60.9%) decreased	23.7±2.9 27.0±3.6 26.6±3.5
Tabbal (2007)[34]	n=72 (41 M, 31 F) Age 63.0 ± 8.2 yr PDD 14.5 ± 6.5 yr	n=38 without follow-up data	Day of surgery 6.2±2.6 mo post-	 +5.1±0.7 median 3.7 (range -3.6 to +23.9)	n/a
Bannier (2009)[24]	n=22 (15 M, 7 F) Age 60.5 ± 1.4 yr PDD 9.8 ± 0.6 yr	Severe depression, diabetes, thyroid disease, pre-menopausal	1 mo pre- 3 mo post- 16 mo post-	 M: +3.5±0.7, p<.001 F: +2.6±0.8, p=.018 M: +6.2±1.1, p<.001 F: +5.5±1.2, p=.028	M: 24.9±0.6 F: 24.2±1.8 M: 26.0±0.5 F: 25.3±1.5 M: 26.9±0.6 F: 26.4±1.4
Guimarães (2009)[23]	n=41 (17 M, 24 F) Age 60.0 ± 6.7 yr PDD 14.0 ± 6.9 yr	None	Day of surgery 2.5±1.6 yr post-	 +13.2±10.0%	23.3±4.0 26.8±3.0
Sauleau (2009)[16]	n=32 (21 M, 11 F) Age 57.7±8.2 yr PDD 11.9±3.9 yr	None	Day of surgery 3 mo post- 6 mo post-	 +5.7±5.4 24 (75%) increased, 2 (6.3%) decreased	22.9±0.8 24.2±0.8, p<.0001 24.9±0.9, p<.005
Moghaddasi (2010)[22]	n=15 (14 M, 1 F) Age 51.8 ± 8.3 yr PDD 8.5 ± 1.5 yr	None	Day of surgery 1 mo post- 3 mo post-	 +3.3±2.6, p<.001 +5.9±3.7, p=.037	n/a
Strowd (2010)[18 a]	n=88 (54 M, 34 F) Age 67.5±9.0 yr PDD 11 yr	Post-operative complications such as infection or bleeding Multiple targets	Day of surgery 2 mo post- 5 mo post- 11 mo post- 24 mo post-	 +2.5 (no sd), p=.1024	n/a
Escamilla-Sevilla (2011)[21]	n=14 (12 M, 2 F) Age 58.0 ± 13.2 yr PDD 11.7 ± 3.9 yr	n=6 (1 intracranial hemorrhage, 1 skin infection, 4 refused)	1 week pre- 3 mo post- 6 mo post-	 +5.5±6.3, p=.006	25.3±3.8 26.5±3.4
Genty (2011)[36]	n=53 (35 M, 18 F) Age 59.9 ± 8.3 yr PDD 11.5 ± 4.2 yr	None	1 mo pre- 6 mo post-	n/a	OA pain 23.2±2.8 No OA pain 23.9±4.2 OA pain 25.1±3.2 No OA pain 26.0±4.0
Lee (2011)[17]	n=25 (17 M, 8 F) Age 61.1 ± 1.1 yr PDD 12.7 ±1.4 yr	None	Day of surgery 3 mo post- 6 mo post- 12 mo post- 24 mo post-	 +5.6±2.1, p<.001	n/a
Rieu (2011)[30]	n=22 (10 M, 12 F) Age 60.7 ± 1.5 yr PDD 9.6 ±0.9 yr	None	1 mo pre- 3 mo post- 6 mo post- 12 mo post-	 64.1±4.5 67.7±4.3, p<.05 69.6±4.3, p<.05 72.5±4.5, p<.05	22.9±1.2 24.2±1.2, p<.05 24.9±1.3, p<.05 26.0±1.3, p<.05
Serranová (2011)[38]	n=20 (20 M) Age 58.3 ± 6.0 yr PDD 15.7 ± 4.0 yr	None	Day of surgery 2.8±2.1 yr post-	 91.5±11.0 83.4±14.0	n/a
Arai (2012)[37]	n=16 (7 M, 9 F) Age 64 ± 6.9 yr PDD 13.7 ± 4.6 yr	Severe liver dysfunction, renal failure, cardiopulmonary disease, uncontrolled diabetes, GIT disease	Day of surgery 3 mo post-	 +3.8±1.0, p=.0054 (+6.5±7.3%) 12 (75%) increased (>.05kg)	n/a
Jorgensen (2012)[20]	n=10 (7 M, 3 F) Age 61.7 ± 6.5 yr PDD 13.3 ± 4.8 yr	n=3 (1 deceased, 1 cerebral hemorrhage, 1 refused)	Day of surgery 3 mo post- 12 mo post-	 +4.7 (range 2.0 – 11.5), p<.05	25.5±0.9 26.5±0.8, ns 27.0±0.8, p<.05

Chart continues on page 7.

Table 1: continued from page 6.

Markaki (2012)[19]	n=23 (15 M, 8 F) Age 65.2 ± 8.9 yr PDD 12.7 ± 6.0 yr	Diabetes, thyroid disease, severe depression	3 days pre- 3 mo post- 6 mo post-	79.1±21.0 82.2±22.1, p=.009 17 (73.9%) increased, 5 (21.7%) decreased 82.2±21.0, p=.013 16 (69.6%) increased, 6 (26.1%) decreased	28.7±4.8 29.8±4.8, p=.007 29.7±4.4, p=.025
Růžička (2012)14	n=20 (14 M, 6 F) Age 56.6 ± 5.8 yr PDD 13.2 ± 4.5 yr	None	Day of surgery 1 mo post- 2 mo post- 4 mo post- 6 mo post- 12 mo post- 18 mo post-	 +6.9±4.5, p<.001 18 (90%) increased	n/a
Bilateral VIM					
Strowd (2010)[18 a]	n=11 (8 M, 3 F) Age 69.0 ± 8.0 yr PDD 6 yr	Post-operative complications such as infection or bleeding Multiple targets	Day of surgery 2 mo post- 5 mo post- 11 mo post- 24 mo post-	 +3.5 (no sd), p=.0366	n/a

DBS=deep brain stimulation; F=female; GIT=gastrointestinal; GPi=global pallidus internus; M=male; mo = month; ns=not statistically significant; OA=osteoarthritis; PDD=Parkinson's disease duration; STN=subthalamic nucleus; VIM= ventral intermediate nucleus of the thalamus; yr=year. All weight changes are reported differences from the day of surgery. All values are mean±standard deviation unless stated otherwise.
Ranges are listed when standard deviations were not available, but the study provided range values. Where significance values are not included, the study did not report them.
[a] Included unilateral and bilateral VIM and STN patients, presented all data as a group so cannot report differences between type of surgery
[b] Stimulation was initiated at 1.5 months following surgery
[c] Converted pounds as reported in the publication to kilograms to allow for comparison between studies

Weight changes

All of the studies reported post-operative weight gain, either as changes in weight or BMI (Table 1). This increase was reported as statistically significant at 12 months[15] and 24 months[17] post-operatively for unilateral STN-DBS. For bilateral STN-DBS, weight gain was reported as statistically significant at 1 month,[22] 3 months,[19,22,24,26,30,37] 6 months,[19,21,27,30] 12 months,[20,28,30,32] 18 months,[14] 19 months,[25] 23 months,[13] 24 months,[17] 25 months[31] and 31 months[25] post-operatively, and significant increases in BMI were reported at 3 months,[16,19,26,30] 6 months,[16,19,27,30] 12 months.[20,28,30] One study reported that weight gain at 24 months was not statistically significant.[18] Jorgensen et al (2012)[20] reported that BMI changes were significant at 12 months following STN-DBS but not at 3 months.

Weight gain occurred for 64.5% with bilateral GPi-DBS[16] and between 62 and 100% with bilateral STN-DBS.[13,14,16,19,25,27–29,35,37] Following bilateral GPi-DBS, 35.7% lost weight[16] and, with bilateral STN-DBS, between 6.3 and 26.1% lost weight.[13,16,19,27] Between the first measurement at 19 months and the second measurement at 31 months, Novakova et al (2007)[25] reported that 26.1% gained weight and 60.9% lost weight.

According to one study, waist circumference increased significantly at 3 months, 6 months and 12 months post-operatively (88.3±3.6 to 91.5±4.9kg (3mo), p<.05, to 93.2±4.1 (6mo), p<.05, to 96.2±3.7 (12mo), p<.05).[30]

Five studies reported differences in body composition.[19–21,24,26] At 3 months, three studies reported a significant increase in fat mass (24.1± 9.6 to 24.8± 9.8kg, p=.05;[19] 19.6±1.9 to 22.6±2.3kg, p<.05;[20] males 17.2±1.4 to 18.4±1.4kg, p<.05 and females 20.4±3.6 to 22.9±3.0kg, p<.05[26]) while one reported that fat mass had not increased significantly (males +9.2±3.3%, ns and females +20.0±8.0%, ns[24]). At 6 months, one study reported a significant increase in fat mass (19.6±1.9 to 23.5±2.5kg, p<.05[20]) while two reported that change in fat mass was not significant (17.9±13.8% to 19.0±9.8%, p=.763;[21] 24.1± 9.6 to 26.3±10.2kg, ns[19]), one of which reported a significant increase at 3 months.[19] At the 16 month measurement, Bannier et al (2009)[24] reported that fat mass significantly increased in males (+5.9±1.3%, p<.001) and in females (+30.2±14.1%, p<.01).

Jorgensen et al (2012)[20] reported that fat free mass did not increase at 3 months or 6 months (58.9±3.7 to 60.1±3.6, ns to 60.6±3.2 kg, ns). In other studies, when stratified by gender, males had a significant increase in fat free mass at 3 months (59.7±1.4 to 61.7±1.3 kg, p<.0001;[26] +3.9±0.7%, p<.0001[24]), 6 months (+2.2± 4.0 kg, p=.04[19]) and 16 months (+19.2±5.2%, p<.01[24]) post-operatively. Females did not experience significant changes in fat free mass at 3 months (42.0±1.8 to

Table 2: Characteristics of 14 studies reporting weight gain as an adverse event following DBS surgery for Parkinson's disease

First author (year)	Participant characteristics	Measurement method and frequency	n (%) experiencing weight gain
Bilateral GPi-DBS			
Volkmann (2001)[49 a]	n=11 Age 56.6 ± 9.4 yr PDD 10.5 ± 2.7 yr	Method not reported 1 yr post-	11 (27)
Bilateral STN-DBS			
Limousin (1998)[48]	n=24 (11 M, 13 F) Age 56.0 ± 8.0 yr PDD 14.0 ± 5.0 yr	Method not reported 1 yr post-	18 (90)
Volkmann (2001)[49 a]	n=16 Age 60.2 ± 9.8 yr PDD 13.1 ± 5.9 yr	Method not reported 1 yr post-	6 (38)
Figueiras–Méndez (2002)[47]	n=22	Method not reported 2 yr post-	16 (73)
Martínez-Martín (2002)[44 a]	n=17 (12 M, 5 F) Age 60.9 ± 7.7 yr PDD 16.4 ± 8.5 yr	Method not reported 0.5 yr post-	2 (12)
Valldeoriola (2002)[45]	STN - medication n=10 Age 59.2 ± 8.7 yr PDD 15.6 ± 10.3 yr STN + medication n=16 Age 61.7 ± 6.3 yr PDD 14.6 ± 6.2 yr	Method not reported 18.2 ± 2.1 mo post- 18.7 ± 1.7 mo post-	1 (10) 1 (6.3)
Doshi (2003)[51 b]	n=23 (18 M, 5 F) Age 58.0 ± 9.3 yr	Method not reported 6 mo to 1 yr post-	2 (9)
Krack (2003)[52]	n=49 (24 M, 25 F) Age 55.0 ± 7.5 yr PDD 14.6 ± 5.0	Method not reported 3 mo post- 1 yr post-	41 (84) 39 (80)
Tamma (2003)[46]	n=30	Method not reported 1 yr post-	30 (100)
Schüpbach (2005)[42]	n=37 (24 M, 13 F) Age 54.9 ± 9.1 yr PDD 15.2 ± 5.3	Method not reported 5 yr post-	12 (32)
Visser-Vandewalle (2005)[50]	n=20 (15 M, 5 F) Age 60.9 ± 8.1 yr PDD 15.0 ± 4.4	Self-report 4 yr post-	20 (100)
Guehl (2006)[43 a]	n=44 (31 M, 13 F) Age 58.8 ± 9.2 yr PDD 14.2 ± 5.1 yr	Self-report 3 mo post- 1 yr post-	3 (6.8) 7(15.9)
Derost (2007)[41]	Young group (<65yr) n=53 (38 M, 15 F) Age 57.4 ± 0.7 yr PDD 11.5 ± 0.6 yr Old group (>/=65yr) n=34 (24 M, 10 F) Age 68.9 ± 0.5 yr PDD 12.4 ± 0.7 yr	Method not reported 2 yr post- 2 yr post-	12 (22.6) 3 (8.8)
Piboolnurak (2007)[39]	n=33 (24 M, 9 F) Age 53.4 ± 8.3 yr PDD 13.5 ± 4.7 yr	Method not reported 3 yr post-	16 (48.5)
Romito (2009)[40]	n=20 (11 M, 9 F) Age 56.4 ± 6.9 yr PDD 14.3 ± 6.2 yr	Method not reported 5 yr post-	20 (100)

mo=month; yr=year
[a] only weight gain >10kg reported
[b] only reported "abnormal weight gain": 2 kg within a week post-operatively and 10kg and 12kg at final time point

41.9±2.0 kg, ns[26]), 6 months (-0.86± 2.81 kg, p=.4319) or 16 months.[24]

Gender differences

No significant differences in weight changes between genders were reported by Markaki et al (2012)[19] (M +3.6±5.4kg, F +2.2±4.4kg, p=.20) or Macia et al (2004)[28] (M +12.2kg, F +6.2kg, p=.11). Changes in BMI values between genders were also reported as statistically similar (M +1.1±0.2kg/m^2, F +1.0±0.3kg/m^2).[26] Barichella et al (2003)[29] did report significant differences in weight changes between genders (M +8.9±7.3 kg, F +10.3±4.0kg; p<0.0001) but not when they were expressed as a percentage of starting weight (M +13.3±10.7%, F +18.7±5.3%, ns).

Surgical target differences

Few studies have compared weight outcomes based on the surgical target. Sauleau et al (2009)[16] reported a significantly greater BMI increase with bilateral STN-DBS than with bilateral GPi-DBS (p<.048). Strowd et al (2010)[18] reported significantly greater weight gain at 24 months post-operatively in VIM patients than STN patients (p=.0175) while Lee et al (2011)[17] reported statistically similar weight gain, p=0.885 between unilateral STN-DBS and bilateral STN-DBS (Table 1).

Differences compared to controls

Five studies reported comparisons with control groups (Table 3).[15,17,21,28,30] In two of these, patients with Parkinson's disease eligible for surgery comprised the controls;[21,28] in two others, patients with Parkinson's disease from a registry and matched for age, gender, disease severity and medication acted as controls;[15,17] in the final study, controls consisted of healthy adults who were matched for age

Figure 2

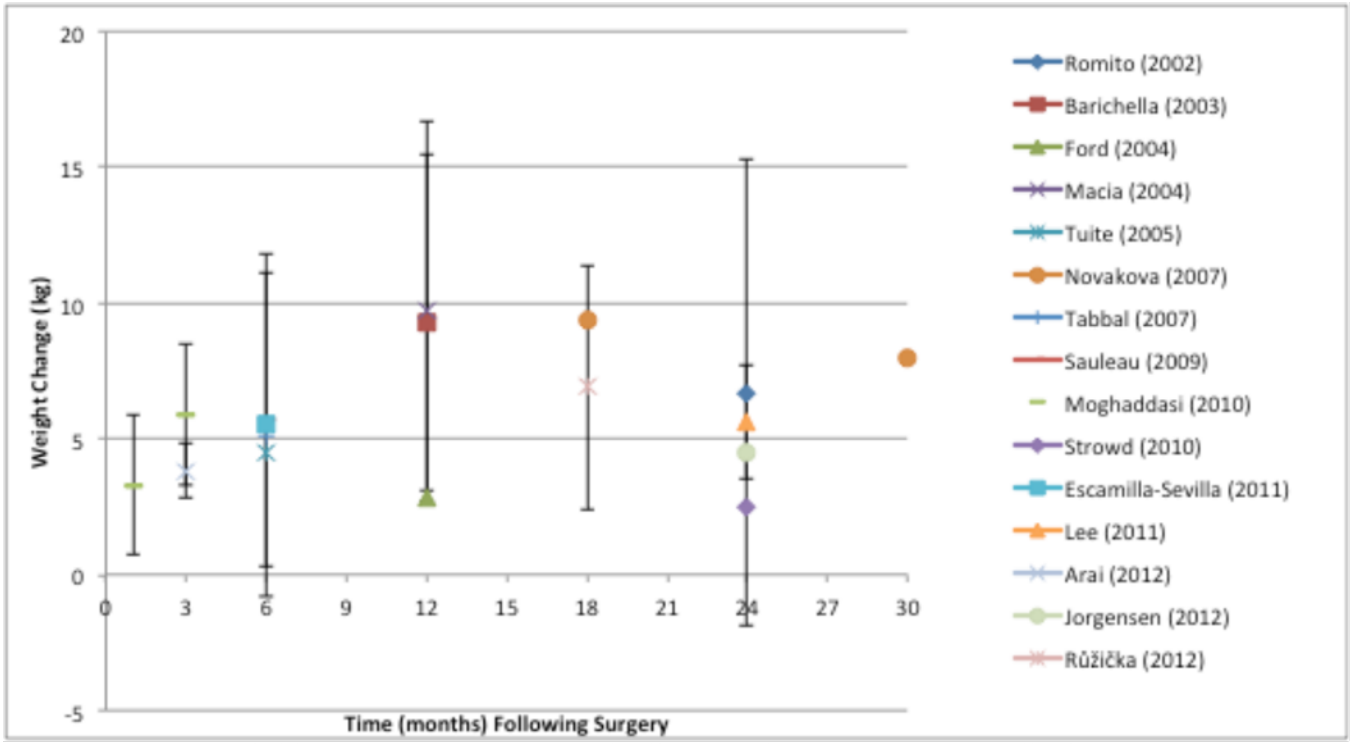

Figure 2: Weight change (kg) following deep brain stimulation (DBS) surgery of the subthalamic nucleus (STN) for Parkinson's disease

Table 3: Differences in weight changes between Parkinson's disease surgical patients and controls

First author (year)	Surgical participants	Control participants	Weight and/or weight differences (kg)
Macia (2004)[28]	n=19 (11 M, 8 F) Age 59.9 ± 6.6 yr PDD 15.0 ± 3.2 yr	n=14 (8 M, 6 F) Age 61.5 ± 59.9 yr PDD 12.2 ± 4.0 yr	At 12 months: Surgical 70.3 ± 14.8 Control 65.8 ± 15.3 ns
Walker (2009)[15]	n=39 (27 M, 12 F) Age 59.1 ± 10.1 yr PDD 11.4 ± 6.1 yr	n=40 (29 M, 11 F) Age 60.7 ± 8.7 yr PDD 10.2 ± 5.2 yr	At 12 months: Surgical +4.3 ± 3.2 Control -0.34 ± 4.1 p<.05
Escamilla-Sevilla (2011)[21]	n=14 (12 M, 2 F) Age 58.0 ± 13.2 yr PDD 11.7 ± 3.9 yr	n=14 (9 M, 5 F) Age 63.6 ± 9.8 yr PDD 14.7 ± 5.5 yr	From baseline to 6 months: Surgical 73.7 ± 13.9 to 77.3 ± 13.9 Control 76.1 ± 11.7 to 76.7 ± 13.1 p=.031 for differences in change
Lee (2011)[17]	n=25 (17 M, 8 F) Age 61.1 ± 1.1 yr PDD 12.7 ± 1.4 yr	n=21 (17 M, 4 F) Age 59.7 ± 1.7 yr PDD 11.4 ± 1.0 yr	At 24 months: Surgical +5.6 ± 2.1 Control -0.8 ± 1.1 p<.001
Rieu (2011)[30]	n=22 (10 M, 12 F) Age 60.7 ± 1.5 yr PDD 9.6 ±0.9 yr	n=22 (10 M, 12 F) Age 60.4 ± 1.3 yr	At 12 months Surgical 72.5 ± 4.5 Control 74.0 ± 4.7 ns

ns=not statistically significant; PD=Parkinson's disease; yr=year; PDD=Parkinson's disease duration

and gender.[30] The PD controls and surgical patients were monitored for the same length of time. Controls tended to maintain weight while the PD surgical patients gained weight. This difference was reported as significant in three studies.[15,17,21]

Time frame of weight gain

Figure 2 outlines the weight gain according to follow-up time following bilateral STN-DBS for those studies that reported average weight change.[13,14,16–18,20–22,25,27–29,32,34,37] While there is wide variation in the amount of weight gained at each time point, the trend indicates that weight gain peaks around 12 to 18 months following surgery and then begins to decrease.

For unilateral and bilateral STN-DBS, it was reported that the majority of the weight gain occurred in the first 6 months[14,15,17] while for others it occurred at 3 months,[19] 12 months[14] or 18 months.[14]

Discussion

Although DBS guidelines and reviews commonly list weight gain as an adverse effect of the surgery, weight changes following DBS surgery have not previously been reviewed systematically. The results of this review indicate that between 62 and 100% of patients gain weight following both STN-DBS and GPi-DBS with significant weight gain occurring as early as one month post-operatively and continuing to increase until 12-18 months post-operatively. At this point, weight may begin to decrease[33] with more patients losing weight than gaining weight.[25] However, overall body weight remained significantly higher than pre-operative values up to 31 months following surgery.[25]

There was wide variation in the amount of weight gained, and there were also reports of between 6 and 26% of STN-DBS patients losing weight within the first year post-operatively. Individual differences and differences in the therapeutic response to the surgery may influence the extent to which weight changes occur. This may also be true for gender, not in terms of weight per se, but for body composition with males more likely to gain fat mass and fat free mass while females may preferentially gain fat mass. Fat mass gains in both genders may increase central adiposity as indicated by the increased waist circumference reported by one study.[30]

Weight gain following DBS is a concern due to increases in fat mass, and particularly abdominal fat mass, which may increase the risk of chronic diseases such as cardiovascular disease and diabetes. This has been investigated in one study to date where, out of 22 STN-DBS patients, five became diabetic and two developed metabolic syndrome.[30]

On the other hand, weight loss in Parkinson's disease has long been documented as an issue. This may particularly be true in those eligible for DBS for whom symptom management is poor and disability is high. Significant weight loss in the months prior to surgery has been reported,[15,27] and malnutrition may frequently occur.[53] It has also been reported that pre-operative weight is inversely correlated with post-operative weight gain.[14,24] Therefore, weight gain following surgery may potentially help to re-establish normal weights and nutritional status but this has not been explored. Some authors have suggested that the weight gain exceeds weight previously lost but have failed to provide information about long-term weight loss prior to surgery.[24,28] Additional weight loss following surgery, as indicated in some of the studies, may also place those patients at risk of malnutrition. Therefore, weight gain and weight loss should be monitored post-operatively.

Potential explanations for weight gain

There is currently no consensus about the mechanisms of weight gain following DBS. The potential causes have not been consistently or systematically studied, resulting only in the ability to speculate as to the mechanisms. The surgery has been reported to improve mobility and reduce "off" times and dyskinesias,[6] and it has been suggested that reduced energy expenditure associated with the reduction in involuntary movements may contribute to weight gain post-operatively.[26,28] Motor symptoms and complications of dopaminergic medication (fluctuations and dyskinesias) improved significantly following surgery in all of the reported studies.

There is general agreement that active DBS stimulation significantly lowers resting energy expenditure (REE) compared to PD patients on pharmacologic treatment[28,54] and when stimulation is turned off.[54] This reduction in REE approximates that in non-PD controls.[54] However, the relationship between REE reduction and weight gain has been explored in only one study, and a greater reduction in REE was

related to greater weight gain.[28] Daily energy expenditure (DEE) was also significantly reduced after surgery[20,26] without a decrease in reported physical activity,[20] and it was similar to that of non-PD controls.[26] There was no correlation between DEE and body weight or fat mass following surgery.[26] However, daily energy intake was not factored into this relationship.

Studies report that daily energy intake was no different following surgery[16,26] or compared to PD controls (with higher energy expenditure).[28,54] With decreased energy expenditure, this may place the patients in positive energy balance. However, one recent study reported a significant reduction in intake following surgery[20] which may result in energy balance and therefore not explain weight gain. The differences here may lie in the method by which intake data was obtained (retrospective vs prospective).

Relationships among many clinical factors and weight gain or BMI changes related to DBS have been explored, many of which have been hypothesized to play a role in weight gain. However, no significant relationships have been found with motor symptom score[14,17,21,25,28,34,43] or activities of daily living score,[43] disease duration[21,26,28,37,43] or age.[14,21,26,28,37,43] It has been suggested that symptom management using levodopa may contribute to weight loss in people with PD.[55] However, only one study in the current review reported an inverse relationship between levodopa dosage and weight change,[28] while the majority reported no correlation.[15,21,25,29,34]

Surgical target

There is a paucity of data concerning GPi-DBS in the general DBS literature,[6,8] and this extends to reports of post-operative weight outcomes. However, available data indicate that the weight increases following GPi-DBS were less than that in STN-DBS despite similarities in food intake.[16] Volkmann et al (2001)[49] also reported that weight gain happened in only 27% of GPi-DBS patients compared to 38% of STN-DBS patients. VIM-DBS may result in greater weight gain than STN-DBS.[18] However, VIM is not a common target for PD because of its limited ability to ameliorate PD symptoms,[6] and this is reflected in the lack of studies included in this review. Therefore, understanding the specific weight-related outcomes of this target may not be a priority. However, understanding the differences among the surgical targets may provide some insight into the reasons why weight gain occurs.

One explanation for differences may be that the drug dosage is rarely reduced to the same extent as STN-DBS[16] following GPi-DBS.[6,8] Therefore, the same improvements in medication complications may not be present. In fact, dyskinesias may persist resulting in increased energy expenditure.[16]

In addition, the STN is involved in the hypothalamic energy balance and motivational process control centers, the stimulation of which may influence adipose storage[19,21] and eating behaviors.[16,19] Previous studies have reported strong desires and compulsions for sweet foods following STN-DBS in rat models[56] and humans.[57] Increased response to food stimuli and reward cues present when only DBS is active are positively correlated with weight gains.[38]

Improved gastric emptying as a result of STN stimulation may also alter hormonal feedback to the hypothalamus and therefore alter appetite.[37] The hypothesis that stimulation of the STN affects adjacent brain structures or tracts involved in the central regulation of energy balance or reward is supported by the fact that the specific location of the electrode within the structure results in differing amounts of weight gain.[14]

Risk of bias

The frequency interval of weight measurement and reporting does not allow for comparison of weight changes at similar times. This also prevents the pooling of the data to determine an overall effect of the weight changes. A number of the studies reported weight changes at an average time post-operatively that included a wide range of months. Given that weight gain might stabilize, followed by weight loss, this may have obscured the true weight changes.

Combining data for both genders may have resulted in body composition changes that were not significant while those that analyzed and reported each separately found gender-specific differences.

As characteristics of those lost-to-follow up and excluded due to incomplete data were not reported, the effect of their exclusion cannot be evaluated. It may be assumed, however, that surgical complications would negate any effects of the surgery and its outcomes on weight and body composition. Inclusion of patients with complications and

subsequent explantation of one or both electrodes in the final data, as was done by Tuite et al (2005),[27] may have introduced confounding.

Limitations

There is limited information in the current literature about long-term weight changes following DBS. The majority reported up to 12 months post-operatively, and longer follow-up indicated that weight begins to decrease again. Whether this change may be due to voluntary or involuntary weight loss has not been reported.

A number of studies reported the collection of data at numerous time points post-operatively but provided only one set of final data, therefore providing limited data with which to plot the trajectory of weight changes. Data was reported for differing lengths of time post-operatively, and this might explain the variation in the results.

Few studies reported the differences in weight changes based on surgical targets or gender. The former may provide information about why weight changes occur and the latter may assist with planning of interventions.

Only one randomized, controlled study conducted to date has evaluated the effect of a 3-month nutrition intervention conducted post-operatively in STN-DBS patients.[23] The use of individualized advice within a protein-redistributed diet (majority of protein intake in the evening) that provided energy in a 65% carbohydrate, 20% fat and 15% protein macronutrient distribution resulted in significantly less weight gain compared to no intervention. This is promising given that it has been reported in another study that reduced energy intake post-operatively still resulted in weight gain.[20] Evidence is still limited, however, in regards to the effectiveness of nutrition interventions post-operatively.

Conclusions and recommendations

Information regarding long-term variations in nutritional status in people with Parkinson's disease is lacking. Modifications of energy metabolism in PD are not well-understood in spite of common beliefs that it may have implications for both weight loss and weight gain, particularly with dopaminergic medication and DBS.[23,54] Further research is required to provide a better understanding of energy metabolism in PD. Longitudinal studies should be conducted to understand the trajectory of weight loss and gain in Parkinson's disease before and after surgical intervention and their acute and chronic effect on health outcomes.

Patients may benefit from dietetic intervention to stabilize weight before and after surgery[10,23] and to ensure a nutritionally adequate diet. Future study on the mechanisms underlying the weight changes would assist with nutrition intervention planning. Until then, dietetic counseling should take into account weight history prior to and following surgery. Excessive weight gain should be managed to avoid potential risk of chronic disease. Long-term monitoring of weight and nutritional status may be required to prevent unintentional weight loss in the years following surgery.

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