Increase in body weight is a non-motor side effect of deep brain stimulation of the subthalamic nucleus in Parkinson's disease

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Abstract

Deep brain stimulation of the subthalamic nucleus (DBS STN) is an effective treatment method in advanced Parkinson's disease (PD) providing marked improvement of its major motor symptoms. In addition, non-motor effects have been reported including weight gain in PD patients after DBS STN. Using retrospective survey, we aimed to evaluate weight changes in our patients with advanced PD treated with DBS STN. We inquired 25 PD patients (16 men, 9 women), of mean age 55 (42–65) years, mean PD duration 15 (9–21) years, who previously received bilateral DBS STN. We obtained valid data from 23 patients. In the first survey, 1 to 45 months after DBS, weight gain was found in all patients comparing to pre-DBS period. The mean increase was 9.4 kg (from 1 to 25 kg). The patients' mean body mass index (BMI) increased from 23.7 to 27.0 kg/m^2, i.e. by 3.3 kg/m^2 (+2 to +6.1 kg/m^2). In the repeated survey one year later, in 12 of the patients body weight moderately decreased, 3 did not change, and 6 patients further increased their weight. Possible explanations of body weight gain after DBS STN include a reduction of energy output related to elimination of dyskinesias, improved alimentation or direct influence on function of lateral hypothalamus by DBS STN.

Abbreviations

DBS STN	- Deep Brain Stimulation of the subthalamic nucleus
PD	- Parkinson's disease
BMI	- Body Mass Index
UPDRS	- Unified Parkinson Disease Rating Scale
MDS	- Movement Disorder Society
LEDD	- Levodopa Equivalent Daily Dose

Introduction

Bilateral deep brain stimulation of the subthalamic nucleus (DBS STN) is an effective treatment method for selected patients with advanced Parkinson's disease (PD), who can not be optimally controlled by pharmacotherapy. DBS is performed using a stimulating electrode stereotactically implanted into an exactly defined target within the brain, and connected to a stimulator generating high-frequency electrical pulses. It has been sug-

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gested that DBS modifies function of the brain nuclei and circuits and therefore influences motor symptoms of the disease. Beside the effects of DBS STN in PD [11], DBS of the internal segment of the globus pallidus was shown to alleviate both symptoms of PD and different dyskinesias, and DBS of the ventral intermedius thalamic nucleus reduces tremor of various origin [3].

DBS STN effectively influences main motor symptoms of PD (tremor, rigidity, bradykinesia) and as a main therapeutic advantage over pharmacotherapy, it improves late stage motor complications of PD. DBS STN directly alleviates motor fluctuations and indirectly, allowing for reduction of antiparkinsonian medication, suppresses dopaminergic induced dyskinesias.

Beside these largely beneficial outcomes, motor as well as non-motor side effects of DBS have been reported. Non-motor effects include occasional behavioral changes, affective and cognitive disorders. In addition, weight gain has been recently reported as an unexpected consequence of DBS [13,2,9,21]. Also in our PD patients, we noticed weight gain following DBS STN [19]. Therefore, the present study was performed in order to evaluate body weight changes in our patients with advanced PD that were treated with DBS STN.

Material and methods

All 25 patients who received DBS STN between 2000 and 2003 in the Movement Disorders Center, Charles University, Prague, were included in the study. They were 16 men and 9 women, mean age in the time of intervention was 55 years (range 42–65), mean PD duration 14 years (range 9–21).

Repeated retrospective survey was used as a method. The mean interval between DBS implantation and the first survey was 19 months (range 1–45). The subjects were provided with a structured questionnaire (44 questions) regarding their family and personal history focusing on potential presence of metabolic syndrome. Further specific questions concerned body weight changes in the period preceding PD, and in the course of PD, before and after the implantation of DBS. All addressed participants returned the questionnaire.

Body mass index (BMI) was calculated from a person's weight in kilograms divided by height in meters squared (BMI=kg/m^2). Accordingly, patients were divided into 6 groups: underweight (BMI under 18.5), normal weight (BMI from 18.5 to 25), overweight (BMI 25–30), 1st degree obesity (BMI 30–35), 2nd degree obesity (BMI 35–40) and 3rd degree obesity (BMI over 40).

We repeated the survey with the same group twelve months later focusing on body weight and metabolic syndrome signs.

All patients were neurologically evaluated using Unified Parkinson Disease Rating Scale (UPDRS) and MDS scale of dyskinesias within one week before and approximately 1 year after DBS STN implantation. Daily doses of dopaminergic medication were converted to Levodopa Equivalent Daily Dose, LEDD (100 mg of standard levodopa equals 150 mg of CR levodopa, 1 mg pergolide or pramipexole, 10 mg bromocriptine, or 6 mg ropinirole).

Body weight values before and after DBS were compared using paired Student's t-tests. Correlations between clinical parameters and body weight changes were calculated using Spearman's rho coefficient.

Results

Within one year from DBS implantation, 23 out of 25 patients did experience motor improvement including alleviation of motor fluctuations and dyskinesias (detailed results of clinical evaluation were published in [19]). Two patients were excluded from the study of body weight changes. One because of discrepancies between the data provided in the patient's questionnaire, our observation, and the data provided by family members. The other one has had DBS interrupted in the time of the first survey as the stimulator was temporarily withdrawn due to inflammatory complications.

Body weight changes

All 23 patients reported body weight gain after DBS implantation (Table 1, Figure 1). In the first survey, we found an overall mean increase in weight of 9.4 kg (range 1–25 kg), i.e. +13%, p<0.0001. In women, there was an average increase in weight of 12.8 kg (range 6–25 kg), i.e. +21%, p<0.01, and in men, weight increased by 7.6 kg (range 1–20 kg), i.e. +10%, p<0.0001. Comparing mean weight increases in men and women, there was a trend towards difference in genders (p=0.07), In the second survey, 14 subjects lost weight, 3 remained stable, and 6 reported further weight gain compared to the first survey. The mean weight change compared to the first survey was –1.4 kg (range –6 to +11 kg) i.e. –2%, p=0.11; –2.4 kg in men (range –6 to +4 kg) i.e. –3%, p<0.01 and +0.5kg in women (range –6 to +11 kg) i.e. +1%, p=0.79. Comparing the second survey to the values before DBS, there was a mean weight gain of 8 kg (from –4 to +24 kg), p<0.0001. With regard to the information on weight preceding the onset of PD, following DBS, there was a mean change of +13 kg (from –4 to +33 kg) comparing to the lowest weight before PD onset and a mean change of +4 kg (from –9 to +25) comparing to the highest weight the patients ever had before PD onset. In this last comparison, body weight increased in 13, decreased in nine, and two patients were unable to state their highest weight before PD.

No significant correlation was found between changes in UPDRS and MDS scores of dyskinesias and weight changes. Nor did we find any significant correlation between weight changes and the changes in LEDD.

After DBS, all patients increased their BMI. The mean BMI before DBS STN was 23.7 (±standard deviation 2.9). In the first survey, it increased to 27.0 kg/m^2 (±3.6) and in the second survey, it remained nearly unchanged at 26.6 (±3.5) kg/m . Shifts in BMI categories occurred, too.

Comparing to BMI values before DBS, in the first survey two patients increased by two BMI categories, 11 patients shifted by one BMI category (one patient increased from underweight to normal weight, 7 increased from normal weight to overweight, and 3 increased from overweight to the 1st degree of obesity). Ten patients did not change their BMI category. In the second survey, 17 patients did not demonstrate any further changes in their BMI category, 2 patients shifted down 1 category (from the 1st degree of obesity to overweight), and 1 patient shifted up one category from the 1st degree of obesity to the 2nd degree of obesity (Figure 2).

Discussion

In this retrospective study, we found weight gain accompanying motor improvement in all 23 patients evaluated after DBS STN. Therefore, we confirm previous findings of weight increase after DBS STN. Similarly to other reports [13,2,9,21], average weight gain was nearly 10 kg. Surprisingly, women in our study tended to gain more weight than men, while in none of the previous reports such difference between genders was found. Weight gain in our patients did not correlate with any of clinical variables reflecting motor improvement neither with reduction of dopaminergic treatment following DBS STN.

We have to admit that due to the method used (retrospective questionnaire) and different intervals for each patient between the implantation and the time of the first survey, our results are not completely comparable with previous reports. However, in our study, we observed patients for a longer period of time and repeated the same survey on the study group one year later. Thanks to this, beside weight gain following DBS, we found out that at longer intervals, it is possible to observe weight

Table 1. Weight changes after DBS

	Before DBS		After DBS: 1st survey			After DBS: 2nd survey		
	Mean weight (kg)	Range (kg)	Mean weight (kg)	Range (kg)	Mean weight change (1st survey – before DBS) (kg)	Mean weight (kg)	Range (kg)	Mean weight change (2nd survey – 1st survey) (kg)
All	71.0	50–96	80.4	58–105	9.4***	79.0	60–100	–1.4
Men	75.9	60–96	83.5	70–105	7.6***	81.1	66–100	–2.4
Women	61.9	50–79	74.6	58–90	12.8*	75.1	60–90	+0.5

***p<0.0001; *p<0.01

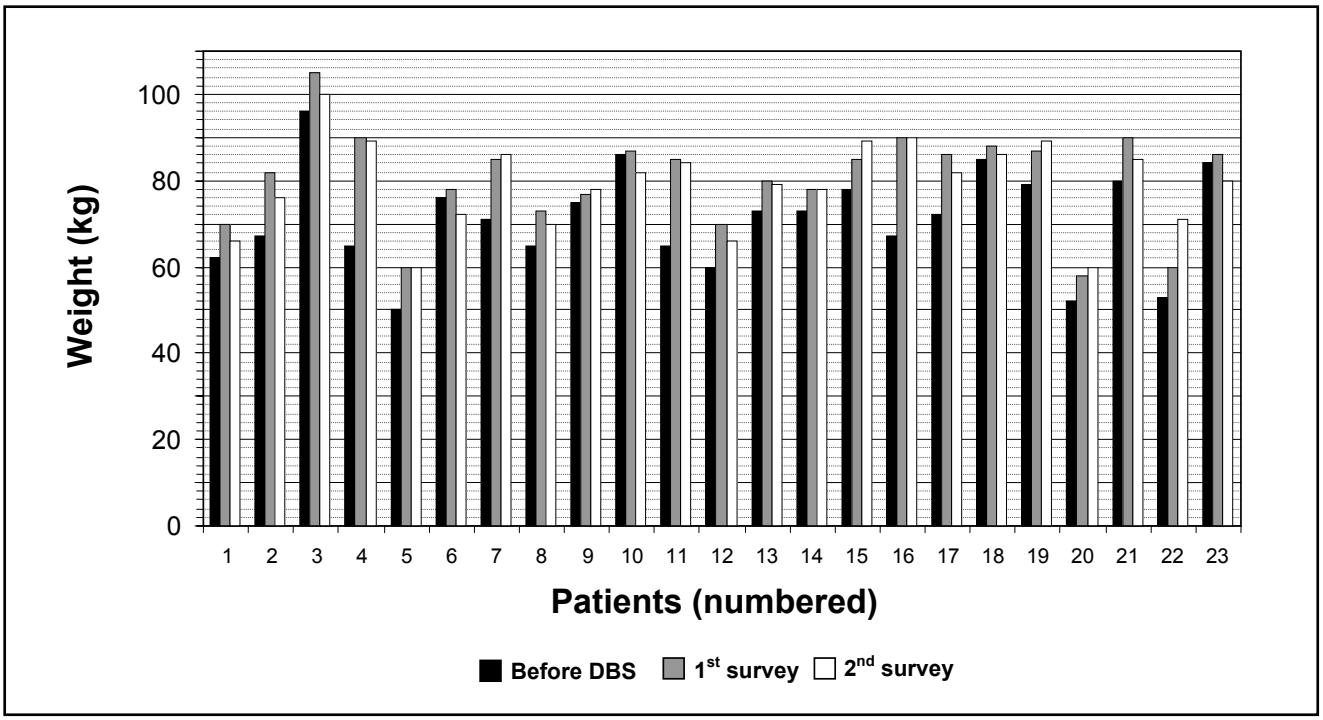

Figure 1. Individual weight changes of the patients before DBS, and after DBS in the first and second survey (kg)

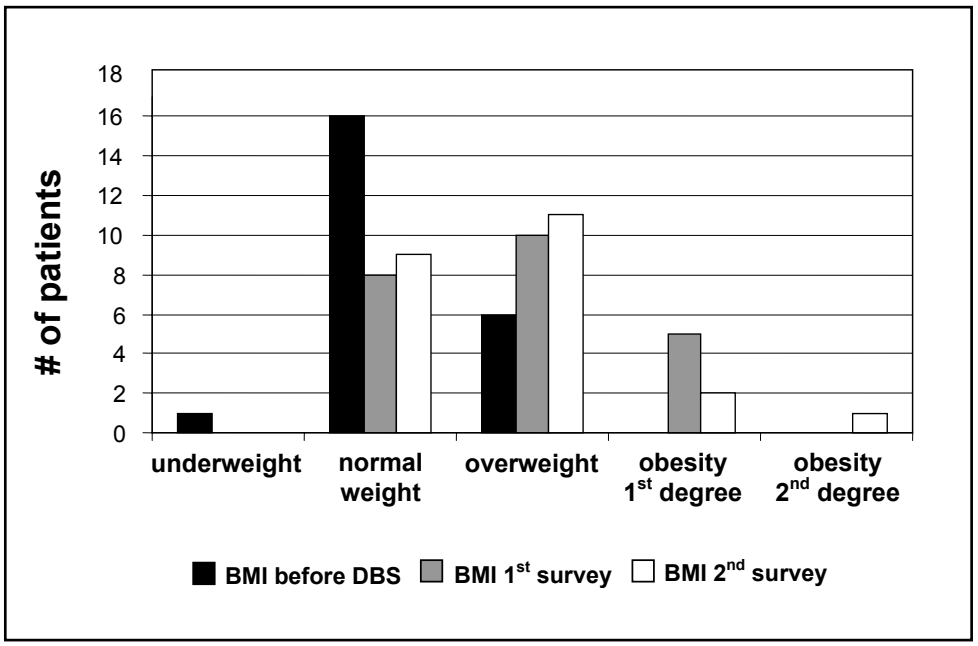

Figure 2. Body Mass Index distribution before DBS, in the first survey and in the second survey. BMI - Body Mass Index

loss reversing the previous weight increase but rarely back to the same level as before DBS. It was unclear how long after the DBS implantation the trend change from increasing to decreasing weight occurred. Possibly, some patients could have already been in a decreasing weight trend when we surveyed them first time, however, they could still report an increase in weight compared to the time before DBS. The weight change interval seems to be very individual. In fact, within 12 months following the first survey, weight increased in three patients with the longest interval as well as in three patients with the shortest interval from the implantation.

In brief, despite different observation methods, the findings from several centers agree in demonstrating weight gain in patients with PD after DBS STN. The mechanism of this weight gain is still unclear and various hypothetical explanations can be suggested.

Firstly, weight gain following DBS STN might reflect a reversal of previous weight loss in PD. Indeed, weight loss has been observed since the early stages of PD and it usually progresses during its course [4,8,15]. According to one study, weight loss in PD patients may begin 2–4 years before the diagnosis is made [7]. One reason for weight loss starting from the beginning of PD may be worsened exploitation of energy from food due to gastrointestinal visceromotor impairment. Accordingly, recent pathologic findings showed involvements of bulbus olfactorius and visceromotor nuclei of the brainstem since the earliest stages of the disease [5]. Also, olfactory dysfunction and motor disability can lead to a decrease of appetite and, in consequence, to a decrease of energetic input [4,1]. However, several studies have reported equal or even higher intake of energy in PD patients compared to healthy subjects [7,20,8]. Surprisingly, according to these studies, energetic input starts to increase when weight begins to decline [4]. The fact that weight loss occurs despite higher intake of energy could mean that it is caused by higher energetic output. This explanation was supported by a couple of studies, which proved that an increase of energetic output was related to severe muscle rigidity [14,10] or dyskinesias, where BMI was negatively correlated with severity of dyskinesias [17]. It was also found that weight loss correlates with the disease severity [4], the degree of hypokinesia [18] or with cognitive decline [12]. Consequently, weight gain can be explained by motor improvement following DBS, especially owing to a reduction in exhausting dyskinesias. Subsequently, the energy output may be reduced, as it was demonstrated in one previous study [13]. Nevertheless, in agreement with our results, the study did not find any correlation between weight gain and the reduction of dyskinesias according to detailed dyskinesia scales [13]. Another study that demonstrated a correlation between weight change and severity of dyskinesias, did so only according to raw UPDRS IV scores that are based on subjective patient evaluation [2].

Secondly, weight gain can be related to changes in medication, especially with regard to a reduction or withdrawal of dopaminergic therapy. It is well known that dopaminergic drugs can cause gastrointestinal discomfort, nausea and vomiting. Therefore, a reduction of dopaminergic drugs might lead to improved alimentation due to an alleviation of the side effects. Nevertheless, neither in our group nor in a previous report [2] patients complained of nausea and vomiting before or after DBS STN. There remains a possibility that dopaminergic therapy can directly influence metabolism and energy consumption. In fact, only a few studies investigated levodopa therapy

in relation to weight in PD patients [18,16]. Palhagen et al. found that patients with an early stage of PD were losing weight even before the initiation of dopaminergic treatment and the loss of weight progressed after levodopa was given [18]. No correlation was found between levodopa dose and weight loss. It was hypothesized that motor improvement induced by levodopa led to changes in energetic input/output ratio. Possible lipolytic or other metabolic effects of levodopa were suggested as well [22]. Consequently, a reduction of levodopa doses would cause weight gain. However, our data do not support this assumption. In accordance to a previous work [2], weight gain did not correlate with LEDD reduction in our patients. In another study, despite a correlation found between LEDD reduction and weight gain, the decreases of LEDD did not correlate with changes in energy expenditure [13].

Finally, weight changes could reflect a direct influence of DBS on autonomous functions and metabolic regulation. The question then would be whether DBS STN specifically normalizes metabolic disturbances induced by PD or it is rather a general effect of stimulation. Despite all the above-mentioned observations, it does not seem that the weight increases following DBS STN in patients with PD reflect just an indirect effect of stimulation related to an improvement of motor disability. In fact, as the patients tend to gain more weight than they ever had, it might reflect a direct metabolic influence of the stimulation rather than just a reversal of pathologic weight loss. In this context, the close anatomic relationship between the subthalamic nucleus and lateral hypothalamus should be taken into account. Hypothalamic pathways and connections of "chemical systems" traverse the medial forebrain bundle in close vicinity to the STN, together with STN connections to the brainstem. Consequently, DBS STN has a chance to influence these pathways as well as adjacent neurons in the lateral hypothalamic area that are involved in feed habits and energy expenditure regulation [6].

In conclusion, DBS STN in PD patients is frequently accompanied by body weight gain. The mechanisms that cause the weight gain are not fully understood. The decrease in energetic output appears as a major contributing factor and may reflect a direct influence of DBS STN on brain systems regulating metabolism and food intake.

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