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Levodopa-carbidopa intestinal gel infusion and weight loss in Parkinson's disease

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Abstract

Introduction: Weight loss (WL) is a frequent yet under-recognized complication of levodopa/carbidopa intestinal gel (LCIG) infusion, as well as a milestone of Parkinson disease (PD) disability progression. The complex association between weight loss, poor nutritional status, motor complications, and PD progression, however, remains unclear.

Methods: Consecutively consenting PD patients treated with LCIG (n= 44; PD duration= 18.3±6.5 years) were enrolled in an open-label observational study assessing the extent of WL occurring during LCIG treatment. As secondary aims, we correlated the nutritional status, as detected by the mini nutritional assessment (MNA), with the severity of motor symptoms (Movement Disorders Society Unified Parkinson's Disease Rating Scale (MDS-

UPDRS) section-III), motor complications (UPDRS section-IV), activities of daily living (Schwab & England scale), cognitive impairment (Mini Mental State Examination - MMSE), depression (Beck Depression Inventory - BDI), difficulties in feeding (Edinburgh feeding evaluation in dementia questionnaire - EdFED-Q), and levodopa equivalent daily dose (LEDD).

Results: There was an average WL of 9.9±10.5% (7.6±7.1 kg) over an LCIG treatment period of 51.6±28.5 months. The extent of WL correlated with the percentage of waking day spent with dyskinesia ($p< 0.05$). The nutritional status correlated with motor symptoms severity ($p< 0.01$), dysphagia ($p< 0.01$), and LEDD ($p< 0.01$).

Conclusion: WL may occur in PD patients undergoing LCIG in correlation with the percentage of the waking day spent with dyskinesia. Regardless of the extent of WL, the nutritional status correlated with higher LEDD, as well as with indexes of disease progression, such as motor symptoms severity and dysphagia.

Introduction

Patients with Parkinson's disease (PD) are consistently reported to be underweight compared to healthy subjects [1]. Weight loss (WL) may begin several years prior to the clinical diagnosis [2] in association with various factors, including PD-associated hyposmia, dysphagia, difficulties in self-feeding, intestinal hypomotility, depression, cognitive impairment, anorexia, and nausea, as well as with increased energy expenditure due to rigidity, tremor, and levodopa-induced dyskinesia [1, 3].

Multiple evidences suggest a key role for WL as a biomarker of disease progression in PD and other neurodegenerative disorders [4, 5]. In fact, the body mass index (BMI), which is calculated as weight in kilograms divided by height in square meters, is a strong predictor of

survival in PD [4, 5]. Moreover, WL correlates with several non-motor complications directly associated with poor PD functional status, such as cognitive impairment and orthostatic hypotension [3].

In previous studies, we found that PD patients treated with levodopa/carbidopa intestinal gel (LCIG) infusion may be particularly susceptible to WL. Causative factors for this phenomenon, however, remain partially unclear and are likely related to a multifactorial interplay between intestinal malabsorption, global deterioration of the overall clinical conditions, and a possible effect of dopaminergic medications on the appetite [6, 7].

The main aim of this study is to evaluate prevalence and severity of WL occurring during LCIG treatment and to analyze the association between the nutritional status of PD patients undergoing LCIG and motor and non-motor indexes of PD disability progression.

Patients and Methods

Inclusion criteria were idiopathic PD, as per the UK Brain Bank criteria [8]; treatment with LCIG for at least 6 months; and availability of weight measurement before starting LCIG. Exclusion criteria were signs or symptoms suggestive of atypical parkinsonism; bariatric surgery; poor general health; and medical conditions potentially associated with pathological WL such as gastroenteric disorders, malignancies, thyroid dysfunction, etc.

As primary endpoints, we measured changes in the body weight and BMI between T0 (about one week, range: 1-7 days, before starting LCIG) and T1 (last outpatient visit on LCIG therapy). Secondary endpoints included the Mini Nutritional Assessment (MNA), an 18-item questionnaire based on anthropometric measurements, eating habits, psychological, and functional aspects associated with nutrition specifically validated for nutritional assessment of community and institutionalized elderly patients [9]; the Edinburgh Feeding Evaluation in

Dementia Questionnaire (EdFED-Q), a 11-items clinical questionnaire assessing behaviours of feeding difficulty (e.g. refusing to eat, turning head away while being fed, spitting out food), nursing intervention (e.g. supervision, physical help) and patient passivity during meals (e.g. spillage, leftover) [10]; the Movement Disorders Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS) part-II, part-III, and UPDRS part-IV; the Mini Mental State Examination (MMSE); the Beck Depression Inventory Scale (BDI); the Schwab and England (SE) scale of activities of daily living (ADL); and the levodopa equivalent daily dose (LEDD), calculated as per a validated conversion table [11] and expressed as LEDD/Kg. Items 32 and 33 of the UPDRS were used to assess the duration and severity of dyskinesia, the MDS-UPDRS item 2.3 to rate the severity of dysphagia. Validated conversion tables were applied to convert data from the UPDRS part-II and -III to the MDS-UPDRS part-II and -III, when needed [12].

All patients were evaluated for peripheral neuropathy (PNP), defined as symmetric alteration of action potential amplitudes or velocities in at least two motor or sensory nerves at the nerve conduction studies (NCS) [13]. PNP were classified as "subclinical" when presenting with electrophysiological alteration not accompanied by clinical symptoms.

The ethical committee approval was obtained (CS2/535; protocol number 0006409) and patients provided written informed consent.

Statistical analysis

Continuous variables were described as mean ± standard deviation. Categorical variables as frequencies or percentage. Changes in body weight between T0 and T1 were calculated as per the following formula: (Δ kg [T0-T1]/body weight at T0)*100). Correlations analyses were carried out using a two-step approach. First, a Pearson's rank correlation coefficient was

applied. Then, data showing significant correlation at the univariate analysis were selected as independent variables in a multiple linear regression model adjusting for PD duration and LCIG treatment duration. Two-tailed p-values lower than 0.05 were considered statistically significant. Analyses were carried out using SPSS 24.0 (SPSS, Chicago, IL).

Results

We enrolled 44 patients, corresponding to 82% of the entire population (n = 54) in active treatment with LCIG at our center. Exclusions were due to poor general health (n = 3 cases), LCIG duration shorter than 6 months (n = 3 cases), lack of data at T0 (n= 2 cases), detainment in prison (n = 1 case), and diagnostic revision into multiple system atrophy (n = 1 case). The duration of LCIG therapy was 51.6 ± 28.5 months (range: 10-120 months). Clinical, demographic, and nutritional data are detailed in Table 1.

There was an average WL of 9.9 ± 10.5% between T0 and T1, corresponding to a weight change greater than 10 Kg in 12 patients (27%); ranging from 6 to 10 Kg in 12 patients (27%); and from 2 to 5 Kg in 6 patients (13%). No significant weight changes were observed in the remaining 16 patients.

At T1, 19 patients (43%) had a BMI < 22 kg/m^2, which is considered the threshold for undernutrition in elderly population; 9 (21%) met the criteria for malnutrition (MNA score < 17) and 6 (14%) required nocturnal enteral feeding to supplement their dietary intake.

Motor complications (UPDRS-IV) improved due to a reduction in the severity of wearing-off, while no significant changes were observed in the duration and severity of dyskinesia (Table 1). The prevalence of PNP increased between T0 and T1, with 8 cases of subclinical PNP becoming “symptomatic”, and 8 cases with normal neurophysiological examination

developing a subclinical PNP (p=0.001; Table 1). The dose of dopaminergic therapies significantly increased between T0 and T1 (p=0.002).

A direct correlation was observed between the extent of WL and the percentage of waking day spent with dyskinesia (β=0.381; p =0.006), and between MNA and the following variables: HY score (β=0.287; p =0.012); dysphagia severity (β=0.227; p =0.007); MDS-UPDRS-III total score at T1(β=0.320; p =0.009); EdFED-Q total score (β=0.320; p =0.008); and LEDD/Kg (β=0.290; p =0.002) (Table 2). Patients developing clinical or subclinical PNP between T0 and T1 showed a worse nutritional status (p=0.005) though not a greater WL.

Discussion

The complex relationship between food intake and weight changes in PD remains unclear. Regardless of food intake, PD patients have lower BMI than healthy subjects [14]. Moreover, a decrease in the BMI correlates with a more aggressive pattern of motor symptoms progression [4], suggesting that PD-associated body weight changes are not necessarily due to reduced caloric intake but may rather correlate with underlying disease mechanisms.

The relationship between WL and PD is even more complex in patients undergoing LCIG. In a previous study, we found that 17% of patients treated with LCIG developed a WL greater than 10kg over a 2-year observational period [6]. Significant changes in body weight were also reported by other authors. Sensi and colleagues described an average WL of 14.7% (10.8 kg) over a 6-year follow-up in patients treated with LCIG, Antonini and colleagues reported a WL of 6.7% over 24 months, and Buongiorno and colleagues a WL of 7% over 22 months [6, 15-17].

To the best of our knowledge, this is the first study specifically investigating factors associated with body weight changes in PD patients with long-term exposure to LCIG. We found that 68% of patients developed a mild to severe WL after 4.5 ± 2.3 years, 27% had a WL greater than 10kg, and 21% met the criteria for malnutrition. After adjusting for LCIG duration, the duration of dyskinesia was the only factor associated with WL, while severity of motor symptoms, dysphagia, and dose of dopaminergic medications correlated with the nutritional status.

Overall, we observed a prevalence and severity of WL that was relatively higher compared to other studies [7, 16, 17], possibly reflecting the greater level of attention devoted to body weight, an outcome frequently neglected or relegated to the role of ancillary measure. However, we cannot exclude the influence of factors such as the long follow-up duration and the inclusion of patients in an advanced stage of disease. Interestingly, we did not find any correlations between WL and disease severity, expressed as motor disability (i.e. SE, HY, MDS-UPDRS-III or ΔMDS-UPDRS-III), cognitive or neuropsychological impairment (MMSE, BDI and MDS-UPDRS items 1.1-1.5), and peripheral nervous system involvement. Instead, we observed an association between WL and the percentage of the waking day spent with dyskinesia. A post-hoc analysis of our data suggests that an adjustment in the dose of dopaminergic therapies for body weight changes might be required to minimize dyskinesia due to a relative LEDD/kg increase, which may ultimately worsen the severity of peak-dose dyskinesia with increased energy expenditure and consequent WL [3, 18]. Also, the relatively low score observed at the EdFED-Q indicates that WL was primarily due to increased energy expenditure rather than feeding difficulties.

Since WL not necessarily implies malnutrition [19], we used the MNA to investigate factors primarily contributing to the nutritional status. Overall, we observed that 43% of patients were at risk of malnutrition and 21% were undernourished. These data are in line with the

published literature, which reports a 0 to 24% prevalence of malnutrition in PD, depending on the study methodology and definition criteria [20]. Interestingly, we found that dyskinesia alone is not a determinant of nutritional status, while disease severity (expressed as HY staging and MDS-UPDRS-III score), dysphagia, feeding difficulties (expressed as EdFED-Q score), dosage of dopaminergic therapies (expressed as LEDD/Kg) and the developing or worsening of a preexisting PNP, correlate with the nutritional state. These data confirm the association between late-stage PD and malnutrition [20]. Of relevance, six of our patients successfully used the PEG-J tube to supplement their daily food intake with nocturnal enteral feeding. Additionally, in spite of the symptomatic LCIG effect on off-time reduction, our data indicate that this device-aided treatment seems to have no beneficial effect on the underlying neurodegenerative disease effect of PD, at least regarding two possible markers of disease progression such as WL and malnutrition. However, this speculation should be confirmed by a case-control study. Finally, an effect of LCIG on the intestinal flora and production of gut hormones affecting hunger cannot be excluded. Small intestinal bacterial overgrowth (SIBO) have been reported to be more common among PD patients if compared to controls [21]. SIBO has been associated to a severe pattern of PD symptoms, motor complications and axial disability, as well as to a possible malabsorption of dopaminergic medications [22]. While the interaction between LCIG and SIBO has not been investigated yet, specific studies seem required when considering the possible susceptibility to changes in the microbiota composition of patients receiving a therapy delivered though a feeding tube and the high frequency of gastrointestinal symptoms observed in association with LICG.

In sum, our data highlight the importance of devoting specific attention, as well as periodic nutritional assessments in patients undergoing LCIG. The assessment of PD patients developing WL should include the evaluation of different possible causes, not only related to dyskinesias or motor complications, but also to dysphagia, cognitive impairment,

hallucinations, apathy, depression, and self-feeding difficulties, which should always be considered in advanced PD. The possibility of nocturnal enteral feeding should also be contemplated as an effective option in LCIG-treated PD patients, since a feeding tube is already available [23].

Several limitations should temper the strength of our conclusions, including the retrospective analysis of data collected as part of an open label observational study, and the lack of a control group treated with oral levodopa. Our main aim, however, was to investigate the prevalence and severity of WL in patients undergoing LCIG treatment rather than comparing LCIG and oral levodopa treatments.

Conclusions

Weigh loss may occur in over 60% of PD patients undergoing LCIG. Special attention is required in patients with dyskinesia, which might account for an increased energy expenditure. Clinicians should also consider that nutritional status of PD patients is independently related to indexes of disease progression such as motor symptoms severity and dysphagia. Periodic nutritional assessments seem required to identify patients that could benefit from additional enteral feeding. In addition, a reduction in the LCIG dose might be required to adjust for changes in the LEDD/kg ratio in patients developing WL.

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LEGEND FOR TABLES

Table 1. Demographic, clinical and nutritional data of PD patients in treatment with LCIG.

	Baseline (n=44)	**Follow-up (n=44)**	**P - value**
Age (yrs)	67.4 ± 5.8	71.7 ± 6.6	/
Women (n/total (%))	15/44 (34%)	/	/
Age at disease onset (yrs)	53 ± 7.8	/	/
Disease duration (yrs)	14 ± 5.8	18.3 ± 6.5	**<0.001**
Duodopa therapy duration (months)	/	51.6 ± 28.5	/
LEDD LEDD/Kg	1421 ± 335 20.5 ± 6	1533 ± 474 24.6 ± 8.4	0.069 **0.002**
Clinical Phenotype n (%)	AK= 34 (77%) TD= 10 (23%)	/ /	
HY Number per stage	3 ± 0.9 2= 18; 3=5; 4=21	3.3 ±1.2 2= 17; 3= 4; 4= 14; 5= 9;	**0.003**
SE	63± 13	56 ± 19	**<0.001**
MDS.UPDRS II	17.1 ±.7.2	29.5 ± 9.6	**<0.001**
MDS.UPDRS III	31±12.4	49.2 ±15	**<0.001**
UPDRS IV, Total score (items 32–42) Dyskinesia duration (Item 32) Dyskinesia disability (Item 33) Off state duration (Item 39)	9.5 ± 3.1 1.7 ± 1 1.2 ± 1.2 2 ± 0.6	6.1 ± 2.4 1.7 ± 0.8 1.2 ± 0.8 0.8 ± 0.5	**<0.001** 0.7 0.9 **<0.001**
MMSE	27.2 ± 2.4	24.1 ±4^	**<0.001**
BDI	14.5 ± 7.8	18.5 ±9.5^	**0.01**
WL (kg) – n (%) % WL (ΔWL/weight at T0)	/ /	7.6 ± 7.1 – 30 (68%) 9.9 ± 10.5	/

WL ≥ 10kg, n (%)	/	12 (27%)	
BMI (Kg/m^2) BMI < 22 kg/m^2, n (%)	26.1 ± 4.6 7 (16%)	23.1 ± 4.1 19 (43%)	**<0.001**
MNA total score MNA classification, n (%)	NA NA	20.6 ± 4.5 Normal nutrition status: 16 (36%) Undernutrition risk: 19 (43%) Undernutrition state: 9 (21%)	/
EdFED-Q	/	2.3 ± 3.1	
Excessive granulation tissue, n (%) Device related complications (tube occlusion or stoma infection), n (%)	/	18 (40%) 17 (39%)	/ /
PNP (Total), n (%) Subclinical PNP, n (%) Clinical PNP, n (%)	9 (20%) 8 (18%) 1 (2%)	17 (38%) 8 (18%) 9 (20%)	**<0.001**
Nutrition consultancy, n (%)* Replacement therapy (Vitamin B12 and Folic acid) Oral nutritional supplement, n (%) Enteral feeding, n (%)	000 0 0	17 (38%) 17 (38%) 9 (20%) 6 (14%)	/ / / /

Values are presented as mean ± standard deviation (SD) if not otherwise specified. SE: Schwab and England ADL Scale; HY: Hoehn Yahr Stage; LEDD: Levodopa equivalent daily dose; MMSE: Mini Mental State Examination; BDI: Beck Depression Inventory Scale; MNA: Mini nutritional assessment (total score <17 indicates undernutrition and 17-23.5 undernutrition risk, while over 24 is considered a normal nutritional status); BMI: body max index; EdFED-Q: Edinburgh Feeding Evaluation in Dementia Questionnaire; PNP: peripheral polyneuropathy; (*): at least one nutrition consultancy since LCIG treatment onset; (^): one patient did not succeeded in filling out the MMSE and BDI a T1 due to a severe dementia.

Table 2. Univariate analysis and multiple linear regression analysis for weight loss and nutritional status

	Univariate analysis	
	% of Weight loss*	
	R	**P - value**
ΔLEDD/Kg	0.479	0.01
LEDD/Kg	0.336	0.02
UPDRS part IV	0.481	0.001
"Dyskinesia duration"(item 32)	0.563	0.001
"Off-state duration" (item 39)	0.40	0.007
MNA score	0.408	0.006
	Multiple linear regression analysis	
Co-variable	**β**	**P - value**
"Dyskinesia duration" (item 32)	0.408	0.033
	Univariate analysis	
	MNA score^^	
	R	**P-value**
HY	0.663	<0.01
SE	0.575	<0.01
MDS-UPDRS-III	0.527	<0.001
UPDRS-IV	0.4	0.07
"off-state duration"(item 39)	-0.318	0.035
Dysphagia severity (MDS-UPDRS item 2.3)	-0.482	0.001
Cognitive/mood profile (MDS-UPDRS items 1.1-1.5)	-419	0.005
EdFED-Q	-0.684	<0.001
MMSE	0.499	<0.001
LEDD/Kg	-0.398	0.07
ΔWL	-0.315	0.015

	Multiple linear regression analysis	
Co-variables	**β**	**P - value**
HY	0.308	0.014
Dysphagia severity (MDS-UPDRS item 2.3)	0.236	0.012
MDS-UPDRS-III	0.348	0.015
EdFED-Q	0.331	0.017
LEDD/Kg	0.309	0.002

(*) At the univariate analysis, no correlations were found with age, gender, clinical phenotype, disease duration, MMSE, BDI, LCIG treatment duration, dysphagia severity (MDS-UPDRS item 2.3), cognitive/mood profile (sum of the MDS-UPDRS items 1.1- 1.2- 1.3 -1.4-1.5), constipation severity (MDS.UPDRS item 1.11), "dyskinesia disability" (item 33), SE, HY, MDS-UPDRS-III, ΔMDS-UPDRS-III, MMSE, the use of enteral feeding and the occurrence of device related complications. **(^^)** In addition, no correlations were found with age, gender, BDI, LCIG treatment duration, disease duration, dyskinesia duration and disability, the use of enteral feeding and the occurrence of device related complications at the univariate analysis. Significant variables have been reported for the results observed at the multivariate linear regression analysis. R^2 of the model was 0,5 and 0,865 for WL percentage and MNA score, respectively.