Clinical Nutrition ESPEN 64 (2024) 425–434

Contents lists available at ScienceDirect

Clinical Nutrition ESPEN

journal homepage: http://www.clinicalnutritionespen.com

Original article

Metabolic biomarkers of appetite control in Parkinson's disease patients with and without cognitive impairment☆

Mario Siervo [a, b, *, 1], Fionnuala Johnston [c, 1], Emily Calton [d, e], Anthony James [a], Blossom C.M. Stephan [b], Amanda K.E. Hornsby [f], Jeffrey S. Davies [f], David Burn [g]

[a] Curtin School of Population Health, Faculty of Health Science, Curtin University, Perth, Western Australia, Australia
[b] Dementia Centre of Excellence, EnAble Institute, Curtin University, Perth, Australia
[c] Institute of Neuroscience, Newcastle University, Newcastle Upon Tyne, NE4 5PL, UK
[d] School of Allied Health, Faculty of Health Sciences, Curtin University, Perth, Western Australia, Australia
[e] South Metropolitan Health Service, Harry Perkins Institute, Murdoch, Perth, Western Australia, Australia
[f] Institute of Life Sciences, School of Medicine, Singleton Park, Swansea University, Wales, UK
[g] Faculty of Medical Sciences, Newcastle University, Newcastle Upon Tyne, UK

ARTICLE INFO

Article history:
Received 11 August 2024
Accepted 25 October 2024

Keywords:
Parkinson disease
Cognitive function
Energy intake
Biomarkers
GLP-1
PYY

SUMMARY

Background: Appetite dysregulation in Parkinson's Disease (PD) appears to be linked to physical and cognitive deterioration. PD patients with and without cognitive impairment (CI) were compared to an age-matched control group to explore predictors of appetite control in fasting and post-prandial conditions.

Methods: Fifty-five patients were recruited and divided into three groups: twenty controls (age: 74 y, BMI: 25.8 kg/m^2), nineteen PD patients without CI (72.5 y, 25.1 kg/m^2) and sixteen PD patients with CI (74.3 y, 24.0 kg/m^2). Self-reported appetite perception and circulating blood metabolic biomarkers were measured in fasting and over a 3-h post-prandial period. Biomarkers included glucose, insulin, tumour necrosis factor alpha (TNF-α), leptin, acyl-ghrelin, total ghrelin, peptide YY (PYY), glucagon like peptide 1 (GLP-1), insulin growth factor 1 (IGF-1), growth factor (GF) and triglycerides. Patients were then provided with a mixed meal to eat *ad libitum* with the aim to evaluate links between metabolic biomarkers and control of energy intake.

Results: PD patients with CI had a significant lower protein intake (7.4 ± 2.5 g, p = 0.01) compared to controls (21.9 ± 3.1 g) and PD patients without CI (14.3 ± 3.0 g). Post-prandial plasma GLP-1 concentrations were associated with decreased hunger perception (B±SE, −5.3 ± 2.4 mm·h^{-1}, p = 0.04). PYY concentrations were significantly associated with GLP-1 in fasting (r = 0.40, p = 0.005) and post-prandial (r = 0.46, p < 0.001) conditions. In a multivariate model, post-prandial PYY concentrations were a significant predictor of *ad libitum* energy intake in all subjects (B±SE, −87.5 ± 34.9 kcal, p = 0.01) and in patients with PD (B±SE, −106.8 ± 44.9 kcal, p = 0.04).

Conclusions: PYY and GLP-1 appeared to influence appetite control in PD patients and their roles merit further investigation.

1. Introduction

Parkinson's disease (PD) is the second most common neurodegenerative disease after Alzheimer's disease and characterised by motor symptoms, such as bradykinesia, rigidity, and tremor, as well as a range of non-motor symptoms, including cognitive impairment and altered appetite regulation [1,2]. Altered energy balance and consequent weight loss could indicate progression of PD and be linked to an increased risk of cognitive deterioration [3–5]. Weight

☆ The material presented in this manuscript is original and it has not been submitted for publication elsewhere while under consideration for Clinical Nutrition ESPEN.

* Corresponding author. Curtin School of Population Health, Faculty of Health Science, Curtin University, Perth, Western Australia, Australia.
E-mail address: mario.siervo@curtin.edu.au (M. Siervo).

[1] Shared first authors.

https://doi.org/10.1016/j.clnesp.2024.10.167

loss in PD may predispose patients not only to an increased risk of malnutrition, but has been postulated to lead to the worsening of symptoms [6]. The mechanisms behind weight changes in PD are not fully understood and are likely multifactorial. Reduced energy intake (EI) in people with advanced PD was shown in one study conducted in standardised conditions [7]. Studies have also indicated a higher resting energy expenditure in PD patients compared to healthy controls [8,9]. This is not consistently observed with some studies demonstrating a lower energy expenditure associated with the decreased level of physical activity that occurs due to disability in PD [10] and the use of doubly labelled water showed that total energy expenditure was not increased in PD patients, and weight changes were the result of a decreased EI [11].

Neurodegeration in Parkinson's occurs throughout the brain [7]. It is not known whether neurohormonal control of appetite is disrupted in PD or in PD with cognitive impairment (PD-CI). Pleiotropic metabolic hormones such as ghrelin, peptide YY (PYY), glucagon-like peptide 1 (GLP-1), insulin or leptin have been linked to neuroprotective effects on learning and memory [12–15]. PYY is a gut-derived hormone released after food consumption and decreases appetite and gastric motility [16]. Similarly, the incretin hormone GLP-1 promotes insulin secretion and inhibits glucagon release and it has been linked to neuroprotective effects on neurite outgrowth, generation of neurotrophic factors and progenitor cells, apoptosis, neuro-inflammation and integrity of blood–brain barrier [17]. IGF-1 has neurotrophic and neuroprotective functions, and it plays a critical role in brain health and cognitive function [18]. A decrease in plasma IGF-1 concentrations in PD patients was correlated with deterioration of cognitive function and lower gray matter volumes in the insula (L), caudate (R) and anterior cingulate [19].

This study primarily investigated hormones related to energy homeostasis in PD without and with cognitive impairment (PD-CI). It has been proposed that appetite may be compromised in PD, particularly in those with a higher burden of non-motor symptoms [20]. Given the association between weight loss, increasing non-motor symptoms, and the development of cognitive impairment in PD [4,5], we hypothesized that appetite might be diminished in PD-CI patients. Conversely, appetite may be increased, consistent with the observed rise in energy intake (EI) in PD regardless of cognitive status [21]. To date, no studies have examined appetite regulation in PD patients with cognitive impairment. The specific objectives were to explore whether 1) *ad libitum* food intake and perceptions of fullness and hunger following the consumption of a standardised meal differed between patients with PD without cognitive impairment, PD-CI and a group of matched, healthy controls, 2) fasting and post-prandial concentrations of metabolic biomarkers linked to appetite and energy balance regulation differed between groups and 4) metabolic biomarkers were significant predictors of *ad libitum* EI and hunger and satiety perceptions.

2. Methods

Study Design: This was a quasi-experimental study conducted between 2015 and 2017 at the Clinical Ageing Research Unit (CARU) at Newcastle University, UK. Ethical approval was obtained from NRES Committee Northeast, Newcastle and North Tyneside 1 (Approval Number 14/NE/0002).

Subjects: Three groups of participants aged between 60 and 85 years old were recruited into the study including healthy older adults (controls), Patients without cognitive impairment (PD) and PD-CI. All clinical and cognitive assessments were performed by either a neurologist or a geriatrician with expertise in movement disorders. Participants with PD were recruited from the Movement Disorder Service at Newcastle upon Tyne Hospitals NHS Foundation Trust. Healthy controls had no signs or symptoms of movement disorders or dementia and they were spousal or age matched community dwelling adults. Healthy older adults had no evidence of Parkinsonism by history or on examination, no cognitive symptoms and a Montreal Cognitive assessment (MoCA) score ≥26. PD without CI had normal cognition as defined by a MoCA score ≥26 and the absence of functional impairment resulting from cognitive symptoms. The PD-CI group included patients with a MoCA score of 25 or less, with cognitive and neuropsychiatric symptoms. This group included PD patients with dementia and mild cognitive impairment. All PD-CI patients had a history of PD for more than one year prior to the onset of cognitive symptoms. Participants gave written consent to participate in the study or, if lacking capacity, written consent was obtained from an appropriate carer in accordance with the Mental Capacity Act 2005.

Subjects were excluded from participation if they had any of the following: clinically significant depression, diabetes mellitus, smoker, body mass index (BMI) < 18.5 kg/m^2 or ≥ 30 kg/m^2 or weight change > 3 kg over the preceding 3 months, comorbid gastrointestinal disease or other clinically significant comorbid illness, concurrent use of non-selective anticholinergic medications. Previous deep brain stimulation (DBS) procedures were an exclusion criterion for PD subjects as these potentially affect appetite regulation. A detailed description of the inclusion and exclusion criteria is provided in Tables S1 and S2 of the online supplementary material.

2.1. Study protocol

All participants underwent a screening visit and, if eligible, were recruited and invited to the research centre for a 5-h test visit. A timeline of the study protocol and measurements are provided in Fig. S1 of the Online Supplementary Material. The screening visit comprised history and physical examination, including height, weight, BMI, pulse and blood pressure. At the screening visit, severity of motor parkinsonism was measured using the motor section of the Unified Parkinson's Disease Rating Scale (UPDRS III). Global cognition was assessed using the MoCA and mood according to the 15 item Geriatric Depression Scale (GDS 15). Body composition was measured using bioelectrical impedance and the Three-Factor Eating Questionnaire (TFEQ) was employed to assess eating behaviour. Blood tests (urea and electrolytes, liver function tests, full blood count, thyroid function tests, random glucose) were also performed at the screening visit. All results were evaluated by the research team and eligible participants were then asked to attend the test visit within 14 days of the screening visit.

The test visit was scheduled in the morning between 8:00am and 9:00am; all participants were asked fast for at least 12 h and to be “off” their PD medications (i.e. having not taken any of their usual PD medication from midnight of the day preceding the visit). Other medications were taken as usual. Water was allowed up to 2 h prior to testing. Patients were re-weighed if more than 7 days had passed since their screening visit. The duration of the test visit was approximately 5 h and was conducted in a private clinical room. The test visit started with the insertion of a cannula in an antecubital vein for the collection of serial blood samples. A standardised breakfast (~300 kcal, see below for details) with a glass of water (200 ml) was then provided and patients were asked to consume the meal within 20 min. Blood samples were taken prior to the standardised meal (i.e., fasting status) and then at, 5, 15, 30, 60, 120 and 180 min (post-prandial status) for the measurement of circulating metabolic biomarkers including glucose, triglycerides, acylated ghrelin (AG), total ghrelin (TG), leptin, peptide YY (PYY), insulin, insulin-growth factor 1 (IGF-1), growth factor

(GH), glucagon-like peptide 1 (GLP-1) and tumour necrosis factor alpha (TNF-α). A small glass of water (120 ml) was given at 60 min and 120 min for participant comfort. Immediately after the collection of each blood samples, patients were asked to complete a visual analogue scale (VAS) to assess subjective fullness and satiety perceptions in fasting and post-prandial conditions (5, 15, 30, 60, 120 and 180 min). After the collection of the last blood sample, the cannula was removed and patients were invited to consume as much as they wanted (*ad libitum*) of a variety of foods. The food that was not consumed was weighted and energy and macronutrient content of the food eaten during the meal was recorded. The time duration of the meal was also recorded.

2.2. Energy intake assessment

Standardised Test Meal: A standardised breakfast was offered, which included one slice of white toast with butter, one strawberry yoghurt, jam, short bread biscuit and a 200 ml glass of water. The energy content of the meal was 357 kcal, which included 52 g of carbohydrates (208 kcal, 60 %), 8 g of proteins (32 kcal, 10 %) and 13 g of fat (117 kcal, 30 %). Participants were allowed 20 min to complete their meal and were required to eat all of it.

Ad Libitum Test Meal: After the collection of the last blood sample at 180 min and removal of the cannula, participants were provided with an *ad libitum* meal comprising a pre-measured selection of food. They were asked to take their usual PD medications at this time and invited to eat as much as they liked until they were full. Presentation of the meal was standardised and the meal included a medium banana (90 kcal), a chocolate mousse (360 kcal), a bag ready salted crisps (132 kcal), grated cheddar cheese (125 kcal), tomato and mozzarella pasta bake (695 kcal) and a 200 ml glass of water. The energy content of the provided food was 1402 kcal, which included 161 g of carbohydrates (644 kcal, 46 %), 50 g of proteins (200 kcal, 14 %) and 62 g of fat (558 kcal, 40 %). Each food item was weighed before and after the meal to gain an accurate measure of the food ingested. The duration of the meal for each patient was recorded. A digital image of the meal is provided in Fig. S2 of the online supplementary material.

Appetite Perception: A visual analogue scale (VAS) was used to quantitatively evaluate patients' perceptions for hunger and fullness in response to the standardised breakfast. The VAS scale comprises two statements for hunger and fullness, and each incorporated a 100 mm horizontal line marked to gauge responses ranging from "Very little" to "Very much." Patients were asked to mark the line to reflect their perception for each statement, and a ruler was used to measure to quantify the answers. The statements analysed were: "How hungry [or full] do you feel?" The VAS was completed after the collection of each blood sample (i.e., 5, 15, 30, 60, 120 and 180 min).

2.3. Measurements

Body Composition and Blood Pressure: Weight and height were measured to the nearest 0.1 kg and 0.1 cm, respectively and they were used to calculate BMI. Body fat was measured using a leg-to-leg bio-impedance analyser (BC420 MA, Tanita Corporation, Japan). Resting blood pressure was measured in triplicate using a semi-automated BP recorder (Dinamap V100; GE Medical Systems) and the mean of the three records was calculated.

Eating Behaviour and Depression: The TFEQ has been widely applied to assess eating behaviour. The factor analysis identified 51-items from which three factors were extracted to investigate three main areas of human eating behaviour, i.e. cognitive restraint, disinhibition, and hunger. The internal consistency for the restraint, disinhibition and hunger subscales was respectively of 0.93, 0.91 and 0.85 [22]. Depression was assessed using the Geriatric Depression Scale Short Version (GDS), a 15-item test with higher scores indicating an increased probability of depression. A score greater than five was used as a cut off for depression [23].

Cognitive Function: Cognition was assessed using the Montreal Cognitive Assessment (MoCA), which is well validated in PD [24]. This test measures overall cognitive ability across several domains, including short-term memory, visuospatial skills, executive function, attention and concentration, language, and orientation, with a total possible score of 30 points. MoCA scores range from 0 to 30, with higher scores indicating better neurocognitive function. A score <26 is indicative of cognitive impairment [24].

PD Assessment: Motor disease severity was assessed using the movement disorders society unified rating scale (UPDRS) motor section. This assessment is well validated in the PD population [25].

2.4. Biomarker analyses

Samples were used to quantify leptin, insulin, IL-6, PYY, GLP-1, TNF-α and AG using the Milliplex MAP Kit-Human Metabolic Hormone Magnetic Bead Panel 96-well plate multiplex assay. Total ghrelin was assessed using the Human Ghrelin (Total) ELISA Kit (Cat. No. EZGRT-89 K, Millipore). Insulin-like growth factor-1 was assessed using Human IGF-1 DuoSet ELISA kit (cat. No. DY291, R&D Systems). GH was assessed using Human GH DuoSet ELISA kit (Cat. No. DY1067, R&D Systems). Plasma glucose was measured by standard automated enzymatic methods using an Olympus AU 640 analyser (Olympus, Watford, UK) and insulin by immunoassay (ELISA; Dako UK Ltd, Ely, UK). A detailed description of the methods used to measure the metabolic biomarkers is provided in Table S3 of the online supplementary material.

2.5. Statistical analysis

Sample size calculations are provided in Table S4 of the online supplementary material. Q–Q plots and Shapiro–Wilks test were used to check for normality and non-normally distributed variables were log-transformed to normalise the distribution. Areas under the curve (AUC) for the repeated-measurement of appetite perceptions and metabolic biomarkers were calculated using the trapezoidal method. MOCA scores were first reversed and then log-transformed. Descriptive statistics (mean and SD) were used to describe continuous variables and frequencies (%) were used to describe categorical variables. Analyses were conducted on a complete-case basis and a description of the sample size for each variable is provided in Table S5 of the online supplementary material. One-way ANOVA was used to compare the demographic and baseline data between the three groups. Analysis of covariance was used to evaluate differences between groups for *ad libitum* EI, macronutrient and fiber intake after adjustment for cognitive function (i.e., MOCA scores), depression (i.e., GDS score), eating behaviour (i.e., TEFQ score) and medication use. Medication use was recoded into a binary variable if patients were taking at least one medication for PD (yes) or no medications (no). A full description of the distribution of medication use is provided in Table S6 of the online supplementary material. A repeated-measure ANOVA model was used to compare appetite responses and changes in metabolic biomarkers between groups (G), evaluate significant changes over time (T) and assess their interaction (T*G). Analyses were adjusted for cognitive function (i.e., MOCA scores), depression (i.e., GDS score), eating behaviour (i.e., TEFQ score) and medication use. Pearson's correlation analysis was performed to test associations between *ad libitum* EI, appetite perceptions and metabolic biomarkers. Multivariate linear regression was conducted to assess the association between each metabolic biomarker

(independent variable) with *ad libitum* EI (kcal), protein (grams) intake, perceptions of hunger and fulness (dependent variables) after adjustment for cognitive function (i.e., MOCA scores), depression (i.e., GDS score), eating behaviour (i.e., TEFQ score) and medication use (yes, no). Multiple linear regression was conducted to identify predictors of *ad libitum* EI (kcal) and perceptions of hunger (AUC, mm*hr^{-1}) when all metabolic biomarkers were entered simultaneously into the model. Regression models were adjusted for cognitive function (i.e., MOCA scores), depression (i.e., GDS score), eating behaviour (i.e., TEFQ score) and medication use (yes, no). Data analyses were conducted using SPSS-28 for Windows (IBM Corp. Released 2021. IBM SPSS Statistics for Windows, Version 28.0. Armonk, NY: IBM Corp). P value was set at <0.05 for statistical significance.

3. Results

Fifty-eight patients completed the screening and were recruited into the study and fifty-five completed the study. These included twenty controls (age: 74.0 y, BMI: 25.8 kg/m^2), nineteen PD patients without CI (age: 72.5 y, BMI: 25.1 kg/m^2) and sixteen PD patients with CI (age:74.3 y, BMI: 24.0 kg/m^2). A description of the recruitment process is provided in Fig. S3 of the Online Supplementary Material. Groups were matched for age, weight, BMI, FM% and TEFQ total score but groups differed for systolic and diastolic BP, PD duration, MOCA and GDS scores and medication use. PD duration differed between patients with (107.3 ± 59.5 months) and without (85.9 ± 99.3 months, p < 0.001) CI; MOCA scores were significantly lower in patients with (17.3 ± 5.4) compared to PD patients without CI (27.6 ± 1.5) and controls (28.4 ± 1.1, p < 0.001) (Table 1).

Energy and macronutrient intake: EI during the *ad libitum* meal was not different between groups (p = 0.45). Carbohydrate and fat intake (both absolute and percent) did not differ between groups. PD patients with CI showed a significant lower absolute (p = 0.01) and percent (p = 0.03) protein intake compared to the control group (Table 2).

Hunger and fullness: The three groups did not differ for post-prandial fullness (interaction, p = 0.77, Fig. 1a) and hunger (p = 0.95, Fig. 1b) perceptions. The analyses of the AUCs for post-prandial fullness and hunger scores showed a lack of difference between groups for both fullness (p = 0.52) and hunger perceptions (p = 0.24).

Metabolic Biomarkers: Acyl-ghrelin concentrations showed a significant change with time in all groups (p = 0.03) with lower concentrations reached 60 min after the standardised meal (Fig. 2A). However, no significant differences between groups were observed for post-prandial concentrations for acyl-ghrelin (interaction, p = 0.98) and the other metabolic biomarkers including total ghrelin (interaction, p = 0.94, Fig. 2B), PYY (interaction, p = 0.21, Fig. 2C), leptin (interaction, p = 0.98, Fig. 2D), insulin (interaction, p = 0.90, Fig. 2E), GLP-1 (interaction, p = 0.35, Fig. 2F), IGF-1 (interaction, p = 0.95, Fig. 2G), GH (interaction, p = 0.27, Fig. 2H) and glucose (interaction, p = 0.96, Fig. 2I). The AUC for the post-prandial concentrations of metabolic biomarkers was only significant for IGF-1 (p = 0.04, Fig. S4 of the online supplementary material). There were no differences between groups for triglycerides and TNF-α concentrations (data not shown).

Correlation (across all groups): In fasting conditions, acyl-ghrelin was indirectly associated with glucose concentrations (r = −0.32, p = 0.02). Significant direct associations were also found for fasting PYY concentrations which were associated with IGF-1 (r = 0.45, p = 0.005), leptin (r = 0.45, p = 0.005) and GLP-1 (r = 0.40, p = 0.005). In post-prandial conditions, AUC of PYY was directly correlated with GLP-1 (r = 0.46, p < 0.001) and leptin (r = 0.50, p < 0.001) (Fig. 3).

Multivariate Regressions: *Ad libitum* EI was significantly associated with fasting (unstandardised regression coefficient (b) ± standard error (SE) −118.3 ± 65.5 kcal, p = 0.04) and post-prandial (b±SE −67.0 ± 22.1 kcal, p = 0.004) concentrations of PYY. Post-prandial hunger perception (AUC VAS_{Hunger}) was significantly associated with fasting (b±SE −20.7 ± 6.8 mm*hr^{-1}, p = 0.004) and post-prandial (b±SE −7.1 ± 2.2 mm*hr^{-1}, p = 0.003) concentrations of leptin. None of the metabolic biomarkers was associated with *ad libitum* protein intake and post-prandial fullness perception (AUC $VAS_{Fullness}$) (Table 3).

Multivariate regression analyses identified of PYY AUC as a significant predictor of reduced *ad libitum* EI in all subjects (b±SE -87.5 ± 34.9 kcal, p = 0.01) and in subjects with PD (b±SE -106.8 ± 44.9 kcal, p = 0.04). Post-prandial hunger perception (AUC VAS_{Hunger}) was significantly predicted by leptin (b±SE -5.8 ± 2.6 mm*hr^{-1}, p = 0.04) and IGF-1 (b±SE -3.6 ± 1.4 mm*hr^{-1}, p = 0.01) AUCs (Table 4).

Table 1
Characteristics of study population.

	Controls	PD	PD-CI	$P_{Between\ Groups}$
	Mean ± SD			
N	20	19	16	–
Gender (M/F)	11/9	10/9	9/7	0.99
Age (years)	74.0 ± 6.2	72.5 ± 5.5	74.3 ± 6.0	0.50
Weight (kg)	73.0 ± 10.2	69.9 ± 13.2	64.8 ± 10.6	0.11
BMI (kg/m^2)	25.8 ± 2.0	25.1 ± 2.8	24.0 ± 3.3	0.17
FM (%)	28.8 ± 7.2	28.4 ± 8.4	25.4 ± 7.7	0.37
SBP (mmHg)	152.7 ± 23.9	135.4 ± 20.8	123.5 ± 24.5	<0.001
DBP (mmHg)	75.7 ± 9.8	73.4 ± 11.3	64.1 ± 9.6	0.004
TFEQ score	9.6 ± 5.6	8.4 ± 5.0	8.3 ± 4.1	0.71
PD duration (months)	–	69.5 ± 69.0	107.3 ± 59.5	<0.001
MOCA score	28.4 ± 1.1	27.6 ± 1.5	17.3 ± 5.4	<0.001
GDS score	1.3 ± 0.9	2.0 ± 1.4	5.8 ± 2.5	<0.001

SD = standard deviation; N = number of subjects; M = Male; BMI = body mass index; FM = fat mass; SBP = systolic blood pressure; DBP = diastolic blood pressure; TFEQ = three factor eating questionnaire; PD= Parkinson's disease; PD-CI= Parkinson's Disease patients with cognitive impairment; MOCA = Montreal Cognitive Assessment; GDS= Geriatric Depression Scale.

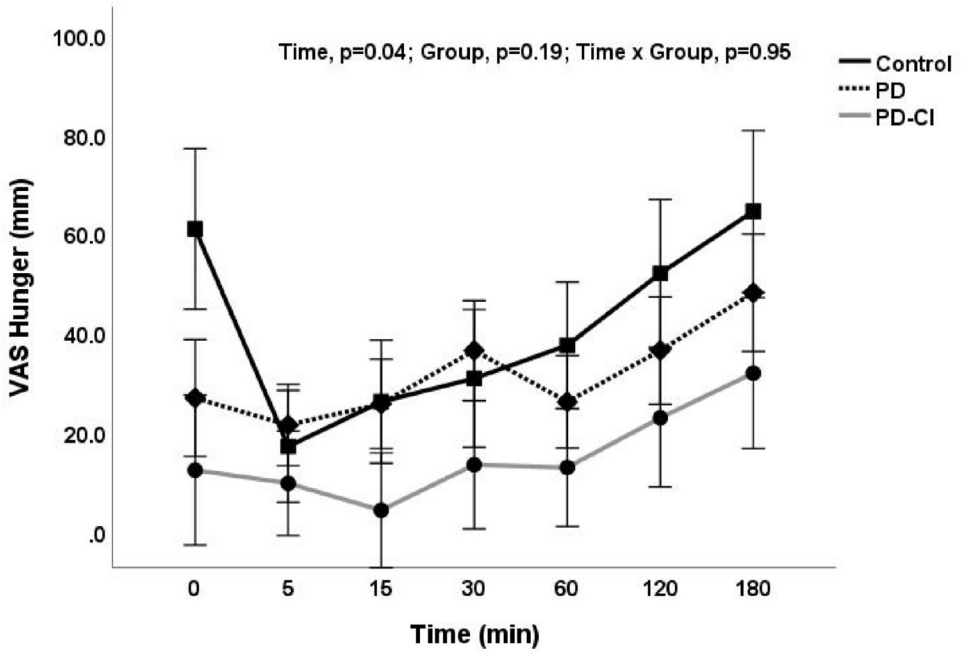
Table 2
Differences in macronutrient and fibre intake during the *ad libitum* meal between healthy controls and Parkinson's disease (PD) patients with and without cognitive impairment (CI).

	Controls	PD	PD-CI	$P_{Between\ Groups}$
Energy intake (kcal)	620.4 ± 174.2	635.0 ± 114.9	441.9 ± 142.3	0.45
Carbohydrate (g)	65.9 ± 20.2	75.8 ± 13.3	56.1 ± 16.5	0.52
Carbohydrate (%)	42.4 ± 7.7	49.6 ± 5.0	56.3 ± 6.3	0.50
Fat (g)	29.9 ± 10.7	30.4 ± 7.1	20.8 ± 8.8	0.15
Fat (%)	44.2 ± 8.2	40.3 ± 5.4	37.4 ± 6.7	0.19
Protein (g)	21.9 ± 3.1	14.3 ± 3.0	7.4 ± 2.5	**0.01**[a,b]
Protein (%)	13.2 ± 1.9	10.5 ± 1.5	6.1 ± 1.6	**0.03**[a]
Fibre (g)	5.6 ± 2.0	5.6 ± 1.3	2.7 ± 1.6	0.28

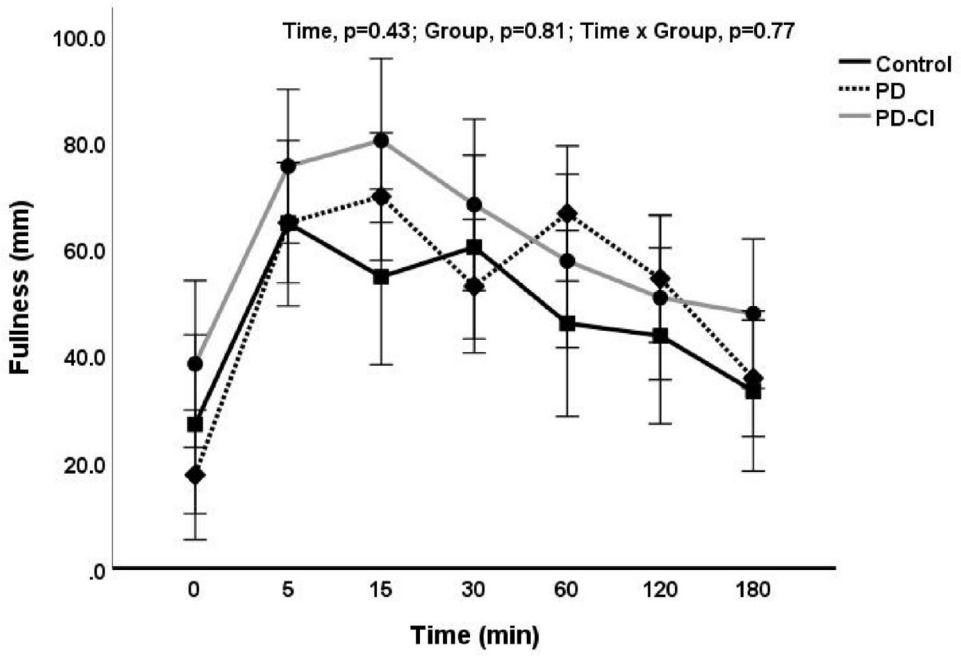
Data is presented as estimated marginal means and error bars are standard errors (SE). Differences between groups were analysed by analysis of covariance (ANCOVA) adjusting for cognitive function, depression, eating behaviour and medication use (see methods for more details). Post-hoc analysis (Bonferroni Test): P < 0.05,[a]Controls *vs* PD,[b]PD *vs* PD-CI,[c]Controls *vs* PD-CI.

4. Discussion

This is the first study to look at EI in PD patients with and without CI. We found no difference in EI between groups, but PD patients with cognitive impairment (CI) showed significantly lower protein intake compared to both control subjects and PD patients



A



B

Fig. 1. Changes in hunger (A) and fullness (B) perception in healthy controls and Parkinson's disease (PD) patients with and without cognitive impairment (CI). Assessments were performed using a 100 mm visual analogue scale (VAS) before (Time 0) and after a standardised test meal at specific time points (5, 15, 30, 60, 120, 180 min). Data is presented as estimated marginal means and error bars are standard errors (SE). Differences between groups were analysed by repeated-measure analysis of variance adjusting for cognitive function, depression, eating behaviour and medication use (see methods for more details).

without CI. Higher levels of post-prandial GLP-1 in plasma were linked to reduced feelings of hunger. There was a significant positive correlation between PYY and GLP-1 concentrations in both fasting and post-prandial states. In the multivariate analysis, post-prandial PYY levels were a significant predictor of *ad libitum* EI in all participants and PD patients.

The two most important metabolic hormones emerging from our analyses are PYY and GLP-1. Peptide YY is produced by the same

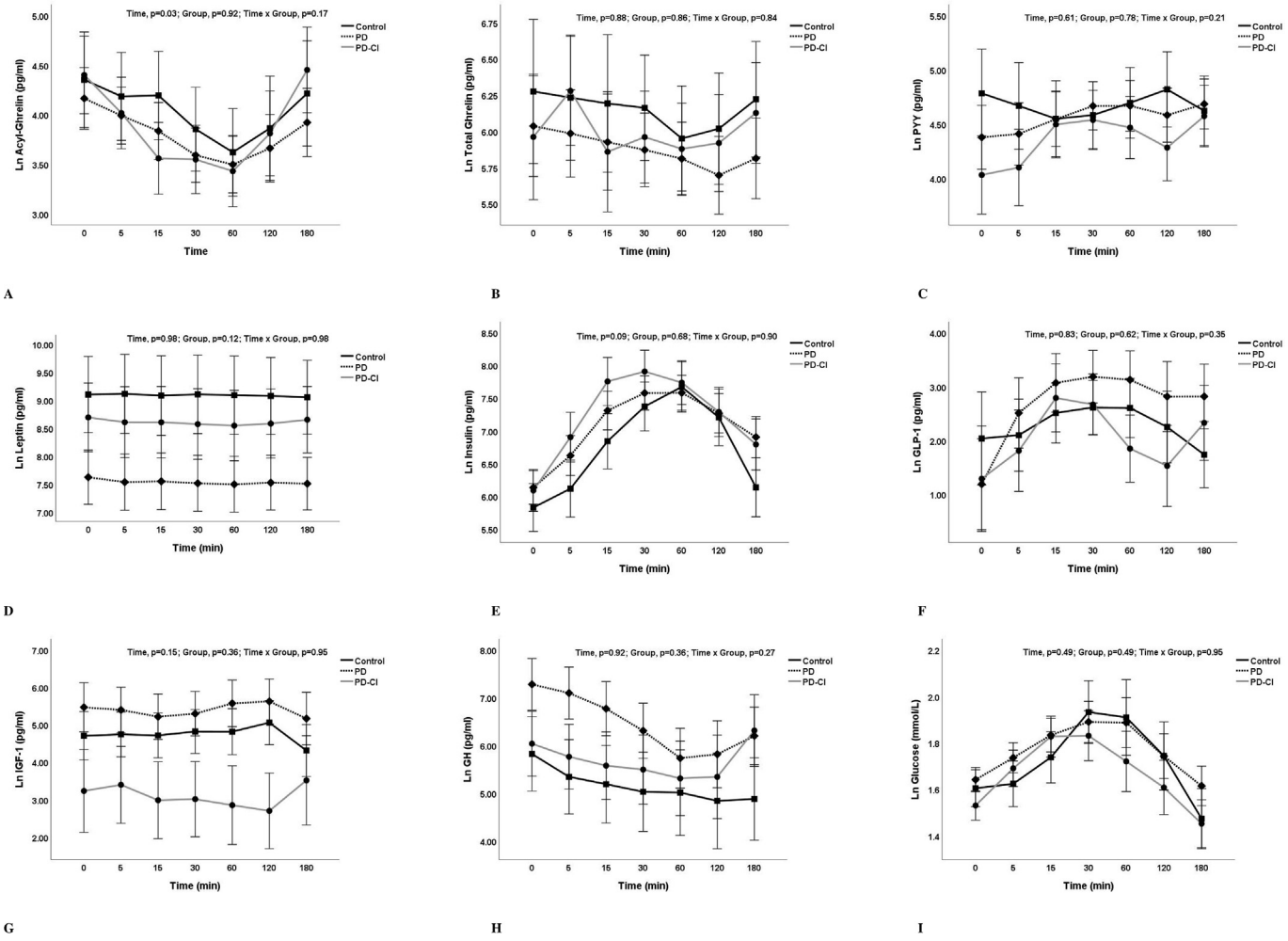


Fig. 2. Changes in plasma metabolic biomarkers in healthy controls and Parkinson's disease (PD) patients with and without cognitive impairment (CI) (Figs. A–I). Measurements were performed after fasting (Time 0) and following the consumption of a standardised test meal at specific time points (5, 15, 30, 60, 120 and 180 min). PD = patients without CI. Data was log transformed before analysis and it is presented as estimated marginal means and error bars are standard errors (SE). Differences between groups were analysed by repeated-measure analysis of variance adjusting for cognitive function, depression, eating behaviour and medication use (see methods for more details). PYY, Peptide YY; GLP-1, Glucagon Like Peptide 1; IGF-1, Insulin Growth Factor 1; GH, Growth Hormone.

L-cells in the GI mucosa that produce GLP-1 which could explain the close correlation observed between these two hormones [26]. PYY reduces motility and slow transit time in both the stomach and the lower GI tract. PYY is secreted in response to the presence of nutrients and bile salts in the lumen of the gastrointestinal tract. It may also be under neural control via the vagus nerve [27]. Levels peak after eating and show a dose response, with higher levels achieved after greater calorie intake [28]. The physiological roles of PYY for the control of appetite in PD patients remains largely unexplored in humans; only one study has been conducted in rats models of PD showing that PYY was involved in the mediation of the effects of electroacupuncture on non-motor symptoms [29].

Glucagon-like peptide 1 (GLP-1) is a short-acting anorexigenic hormone produced mainly in the small intestine in response to vagal stimulation and nutrient ingestion [30]. It increases insulin sensitivity during euglycemia [31], and GLP-1 analogues such as semaglutide are used in the treatment of type 2 diabetes [32]. GLP-1 is rapidly broken down by DPP-4 in the bloodstream [33], and DPP-4 inhibitors such as sitagliptin are also widely used in patients with diabetes [32]. A previous trial in patients with early Parkinson's disease showed that lixisenatide for 12 months delayed the progression of motor disability [34].

There was no correlation between GLP-1 and EI at the *ad libitum* meal. This is unsurprising as GLP-1 predominantly signals satiety, not the initiation of feeding [35]. Intake at breakfast was standardized, and data for GLP-1 during the *ad libitum* meal were not available. There was a positive correlation with PYY, which is expected as both are produced by L cells in the gastric mucosa in response to nutrient ingestion [28].

In a multivariate model we demonstrated that post-prandial PYY concentrations significantly predicted reduced energy intake in all groups. This confirms an intact regulatory role of PYY on energy consumption in weight stable people with PD and PD-CI. Leptin is an anorexigenic hormone produced by adipose tissue [36]. It does not show dynamic variation with meal ingestion, but levels can be increased by prolonged fasting [37]. In our study there was a negative correlation between leptin and hunger as measured by a visual analogue scale for all groups, again suggesting intact signalling in PD and PD-CI in our study group.

PD patients with cognitive impairment (CI) consumed significantly less protein compared to controls and PD patients without CI. This novel finding is not explained in this study but may be clinically relevant due to increased risk of sarcopenia as PD progresses [38], noting that the PD-CI group had a longer disease

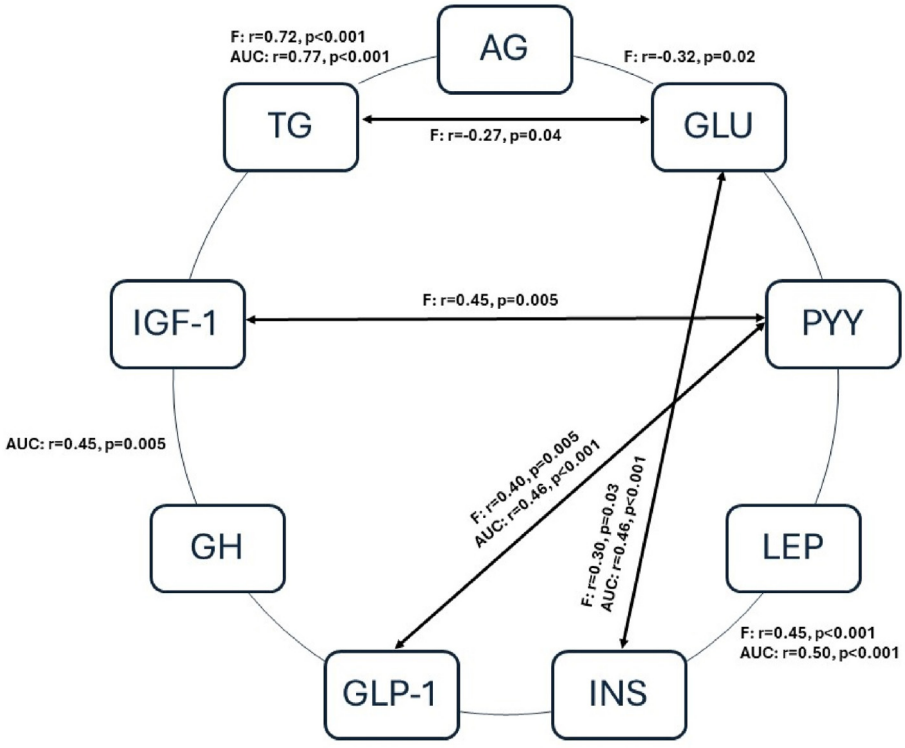


Fig. 3. Description of significant correlations between plasma metabolic biomarkers measured in fasting (F) and post-prandial (Area Under the Curve, AUC) conditions. Data were log transformed before analyses. r = Pearson's coefficient of correlation. AG, Acyl Ghrelin; GLU, Glucose; PYY, Peptide YY; LEP, Leptin; INS, Insulin; GLP-1, Glucagon Like Peptide 1; GH, Growth Hormone; IGF-1, Insulin Growth Factor 1; TG, Total Ghrelin.

Table 3
Linear regression analyses to explore whether fasting and post-prandial plasma concentrations of metabolic biomarkers predicted *ad libitum* energy and protein intake and perceptions of hunger and fullness in health controls and patients with Parkinson's Disease.

	Ad Libitum Energy Intake (kcal)		*Ad Libitum* Protein Intake (grams)		AUC VAS_{Hunger} ($mm \cdot hour^{-1}$)		AUC $VAS_{Fullness}$ ($mm \cdot hour^{-1}$)	
	B ± SE	P	B ± SE	P	B ± SE	P	B ± SE	P
Acyl ghrelin								
Fasting ($pg \cdot mL^{-1}$)	−35.1 ± 54.3	0.52	−0.9 ± 1.0	0.40	13.2 ± 11.2	0.24	16.6 ± 13.9	0.24
AUC ($pg \cdot mL^{-1} \cdot hr^{-1}$)	−12.0 ± 19.3	0.53	−0.1 ± 0.3	0.82	5.9 ± 3.9	0.14	5.9 ± 5.0	0.23
Total ghrelin								
Fasting ($pg \cdot mL^{-1}$)	−78.9 ± 49.8	0.11	−0.86 ± 0.96	0.37	5.9 ± 10.9	0.56	17.2 ± 12.0	0.17
AUC ($pg \cdot mL^{-1} \cdot hr^{-1}$)	−25.5 ± 22.4	0.24	−0.33 ± 0.42	0.42	3.7 ± 4.8	0.39	7.7 ± 5.7	0.17
Peptide YY								
Fasting ($pg \cdot mL^{-1}$)	**−118.3 ± 65.5**	**0.04**	−0.2 ± 1.1	0.82	3.1 ± 12.1	0.79	−11.5 ± 14.6	0.42
AUC ($pg \cdot mL^{-1} \cdot hr^{-1}$)	**−67.0 ± 22.1**	**0.004**	−0.4 ± 0.4	0.35	−2.2 ± 5.0	0.66	0.40 ± 6.4	0.92
Leptin								
Fasting ($pg \cdot mL^{-1}$)	−33.4 ± 34.4	0.33	−0.68 ± 0.67	0.31	**−20.7 ± 6.8**	**0.004**	10.8 ± 8.8	0.22
AUC ($pg \cdot mL^{-1} \cdot hr^{-1}$)	−13.9 ± 11.1	0.22	−0.26 ± 0.21	0.22	**−7.1 ± 2.2**	**0.003**	3.9 ± 2.8	0.17
Insulin								
Fasting ($pg \cdot mL^{-1}$)	11.2 ± 68.7	0.87	0.80 ± 1.31	0.54	−24.2 ± 13.5	0.09	15.5 ± 17.9	0.38
AUC ($pg \cdot mL^{-1} \cdot hr^{-1}$)	−0.5 ± 25.2	0.98	−0.17 ± 0.48	0.72	−8.4 ± 5.1	0.10	5.3 ± 6.3	0.40
Glucagon like Peptide-1								
Fasting ($pg \cdot mL^{-1}$)	−23.4 ± 30.4	0.44	−0.03 ± 0.59	0.95	−2.6 ± 5.7	0.64	−2.1 ± 7.8	0.78
AUC ($pg \cdot mL^{-1} \cdot hr^{-1}$)	−10.0 ± 12.3	0.43	−0.02 ± 0.25	0.91	**−5.3 ± 2.4**	**0.04**	6.1 ± 3.0	0.06
Insulin growth Factor-1								
Fasting ($pg \cdot mL^{-1}$)	21.4 ± 21.7	0.32	0.68 ± 0.40	0.10	3.9 ± 4.0	0.30	−8.5 ± 5.1	0.15
AUC ($pg \cdot mL^{-1} \cdot hr^{-1}$)	8.7 ± 7.2	0.23	0.23 ± 0.14	0.10	1.8 ± 1.2	0.15	−3.2 ± 1.8	0.08
Growth hormone								
Fasting ($pg \cdot mL^{-1}$)	−10.4 ± 31.4	0.73	0.24 ± 0.59	0.68	4.8 ± 6.4	0.49	−3.1 ± 8.6	0.71
AUC ($pg \cdot mL^{-1} \cdot hr^{-1}$)	5.9 ± 9.7	0.54	0.12 ± 0.18	0.49	0.9 ± 2.2	0.61	−1.4 ± 2.4	0.56

Analysis was conducted in all subjects (range of sample size varied for each analyses and ranged between 38 (Fasting Insulin Growth Factor-1) and 55 subjects). Associations were evaluated for biomarkers measured in fasting conditions and following the consumption of a standardised meal. The Area under the Curve (AUC) was calculated as a measure of an integrated post-prandial response of the changes in appetite perception and biomarkers concentrations following the standardised meal. Biomarkers data were log transformed before analysis. Results are presented as unstandardised regression coefficients (B) and standard errors (SE). Regression analyses were adjusted for adjusting for cognitive function, depression, eating behaviour and medication use (see methods for more details).

Table 4
Multiple linear regression to explore the independent prediction of plasma metabolic biomarkers for *ad libitum* energy intake and hunger perception in the whole sample and in patients with a diagnosis of Parkinson's Disease (PD).

AUC ($pg{\cdot}mL^{-1}{\cdot}hr^{-1}$)	All (n = 38)				PD Patients (n = 22)			
	Ad Libitum Energy Intake (kcal)		AUC VAS_{Hunger} ($mm{\cdot}hour^{-1}$)		*Ad Libitum* Energy Intake (kcal)		AUC VAS_{Hunger} ($mm{\cdot}hour^{-1}$)	
	B±SE	P	B±SE	P				
Acyl ghrelin	−18.7 ± 22.3	0.40	6.6 ± 4.0	0.10	−11.5 ± 23.5	0.63	4.2 ± 7.4	0.57
Peptide YY	**−87.5 ± 34.9**	**0.01**	−3.0 ± 6.2	0.62	**−106.8 ± 44.9**	**0.04**	0.6 ± 10.0	0.95
Glucagon like peptide 1	20.2 ± −14.6	0.17	−1.6 ± 2.6	0.54	24.5 ± 17.6	0.18	−1.5 ± 4.6	0.74
Leptin	−27.4 ± 16.0	0.09	**−5.8 ± 2.6**	**0.04**	−17.5 ± 20.0	0.41	−4.9 ± 4.8	0.32
Insulin	19.3 ± 28.0	0.49	1.2 ± 5.0	0.81	13.1 ± 33.5	0.70	0.6 ± 6.8	0.92
Insulin growth factor 1	12.2 ± 7.8	0.13	**3.6 ± 1.4**	**0.01**	15.0 ± 9.5	0.13	2.4 ± 2.9	0.42

Associations were evaluated for plasma biomarkers measured in post-prandial conditions following the consumption of a standardised meal. The Area Under the Curve (AUC) was calculated as a measure of an integrated response of the changes in appetite perception and biomarkers concentrations following the standardised meal. Biomarkers data was log transformed before analysis. Results are presented as unstandardised regression coefficients (B) and standard errors (SE). Regression analyses were also adjusted for cognitive function, depression, eating behaviour and medication (see methods for more details).

duration than people with PD who were cognitively intact. Older adults with PD may experience a reduced protein intake due to multiple factors including dysphagia and difficulties in consuming protein-rich foods, gastrointestinal dysfunction affecting nutrient absorption, medication timing around protein intake (i.e., levodopa competition with dietary amino acids), altered taste/smell perception and depression affecting food interest [39,40]. PD patients are advised to limit protein consumption to improve the bioavailability of levodopa [41]. While the daily protein limit of 0.8 g/kg in the low-protein diet is based on the Recommended Dietary Allowance (RDA), research suggests this minimum threshold may not adequately meet the protein requirements of people with Parkinson's disease [42]. Recent studies indicate that intake above 0.8 g/kg/day might be necessary for this population to reduce the to the risk of sarcopenia and physical disability [43,44]. Further research is required to confirm our results and establish the underlying mechanisms.

Hunger and fullness perceptions were assessed using visual analogue scales. The pattern of hunger between meals was as expected for all groups, with a rapid decline after breakfast and recovery towards the *ad libitum* meal at 180 min. There was no significant difference in hunger responses between groups. Similarly, there was an increase in fullness after eating in all three groups, which declined over 180 min. Again, there was no significant difference in fullness between groups. Our findings align with the original validation study for VAS in 55 healthy men, where hunger reached a nadir 30 min after breakfast and returned to baseline between 180 and 300 min, and fullness peaked at 30 min and returned to baseline at 240 min [45]. It might be possible that the validity of VAS was inadvertently compromised in advanced PD due to guidance from the nurse administering the tool or over-zealous carers. However, hunger AUC was positively correlated with energy intake, and fullness AUC was negatively correlated with EI across the whole cohort. Overall, our results suggest that VAS, though not validated for use in PD or PD-CI, was reasonably accurate in determining feelings of hunger and fullness in this study. Combined with the normal patterns of post-prandial hunger and fullness over time, these data suggest that sensations of hunger and fullness are intact in people with PD and PD-CI. Our results do not support the hypothesis that appetite perceptions are disordered in PD-CI. This is unexpected, as it is intuitive that the number of non-motor symptoms is likely to be higher in the PD-CI group. However, the burden of non-motor symptoms across our cohort was not assessed, and further conclusions cannot be supported.

The design of our study may have confounded our results. Many studies demonstrating increased energy intake in PD have relied on indirect measures of food intake such as food diaries [46], semi-quantitative food questionnaires [47], and food frequency questionnaires [21]. Semi-quantitative food questionnaires and food frequency questionnaires reflect dietary habits over time, rather than discrete eating episodes, while food diaries capture a daily record of energy intake [48]. It is possible that energy intake in PD patients is increased through increased meal frequency rather than increased meal size. Alternatively, intake could be reduced in advanced PD due to cognitive difficulties affecting meal preparation. This study was not designed to measure these factors as food eaten during the *ad libitum* meal was weighed to calculate EI. While this allowed to accurately record exactly what food was eaten during the study, the setting was artificial as participants in PD patients were tested off their usual PD medications. Moreover, participants were offered a standardized range of foods, which may not have reflected their usual diet or food preferences. The *ad libitum* meal was quite large, more than many people would eat in a normal lunch sitting. This may be important as there is evidence that greater portion size results in increased EI, irrespective of body habitus or appetite [49]. A limitation of the study was the absence of data on participants' typical dietary intake and the inability to control for this variable in our analyses. However, the potential confounding effects from dietary differences were minimised by conducting all procedures after a standardized fasting period. Additional, limitations may include the lack of standardisation of the diet the day prior to the test visit and the lack of assessment of appetite perception at the end of the *ad libitum* meal. Another possible confounder could be medication, as both the PD and PD-CI groups had relatively high rates of anorectic medication use. However, all analyses were adjusted for medication use which could have minimised the confounding effects of medication use [21]. Finally, it has been suggested that weight-losing and weight-stable people with PD may be phenotypically different [6,50]. Our study excluded participants with recent weight loss. Our results are consistent with a previous study that showed no difference in energy intake (measured by a 3-day food diary) between controls and patients with PD that also excluded participants with weight loss [11]. As a result, we may not have captured differences in appetite occurring in people with PD and weight loss, who may be at greater

risk of more rapid cognitive decline than their weight-stable counterparts [3].

5. Conclusions

PYY and GLP-1 appeared to influence the control of appetite in PD patients as well as controls. Appetite perceptions are intact in PD and PD-MCI. *Ad libitum* EI did not differ in PD patients with and without CI compared to healthy age-matched controls. Patients with more advanced PD had a significant lower protein intake. Visual analog scales are valid for use in PD and PD-CI. Hormones of energy homeostasis are not disrupted in people with weight-stable PD or PD-CI in the context of an *ad libitum* meal. Patients with PD who lose weight may be phenotypically different to those who do not and were excluded from this study. The potential therapeutic benefits of PYY and GLP-1 analogues in mediating cognitive decline and dysregulated appetite in PD patients warrant further investigation.

Author contributions

M.S., J.S.D. and D.J.B. designed the study. M.S. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis. M.S., F.J. and D.J.B. wrote the manuscript and researched data; A.K.E.H. and J.S.D. conducted the laboratory analyses of metabolic biomarkers. All authors contributed to discussion and reviewed/edited manuscript.

Funding

This study was funded by Newcastle NIHR Biomedical Research Unit.

Declaration of competing interest

The authors have no conflict of interest to declare.

Acknowledgements

The team is grateful to staff of the clinical ageing research unit and movement disorder service at Newcastle upon Tyne Hospitals NHS Foundation Trust including Rachael Lawson, Helen Pilkington, Una Brechany, Tricia McGee, Jane Houghton, Sharon Reading, Naomi Warren, Jane Noble, Paul Goldsmith, Claire MacDonald, Isobel Sleeman and Alex Lehn for referring their patients to the study.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.clnesp.2024.10.167.

References

[1] Hughes AJ, Daniel SE, Kilford L, Lees AJ. Accuracy of clinical diagnosis of idiopathic Parkinson's disease: a clinico-pathological study of 100 cases. J Neurol Neurosurg Psychiatry 1992;55:181–4.
[2] Barone P, Antonini A, Colosimo C, Marconi R, Morgante L, Avarello TP, et al. The PRIAMO study: a multicenter assessment of nonmotor symptoms and their impact on quality of life in Parkinson's disease. Mov Disord 2009;24:1641–9.
[3] Kim HJ, Oh ES, Lee JH, Moon JS, Oh JE, Shin JW, et al. Relationship between changes of body mass index (BMI) and cognitive decline in Parkinson's disease (PD). Arch Gerontol Geriatr 2012;55:70–2.
[4] Lorefält B, Toss G, Granérus AK. Weight loss, body fat mass, and leptin in Parkinson's disease. Mov Disord 2009;24:885–90.
[5] Uc EY, Struck LK, Rodnitzky RL, Zimmerman B, Dobson J, Evans WJ. Predictors of weight loss in Parkinson's disease. Mov Disord 2006;21:930–6.
[6] Sharma JC, Turton J. Olfaction, dyskinesia and profile of weight change in Parkinson's disease: identifying neurodegenerative phenotypes. Parkinsonism Relat Disorders 2012;18:964–70.
[7] Braak H, Del Tredici K, Rüb U, de Vos RA, Jansen Steur EN, Braak E. Staging of brain pathology related to sporadic Parkinson's disease. Neurobiol Aging 2003;24:197–211.
[8] Markus HS, Cox M, Tomkins AM. Raised resting energy expenditure in Parkinson's disease and its relationship to muscle rigidity. Clin Sci (Lond) 1992;83:199–204.
[9] Levi S, Cox M, Lugon M, Hodkinson M, Tomkins A. Increased energy expenditure in Parkinson's disease. BMJ 1990;301:1256–7.
[10] Barichella M, Cereda E, Faierman SA, Piuri G, Bolliri C, Ferri V, et al. Resting energy expenditure in Parkinson's disease patients under dopaminergic treatment. Nutr Neurosci 2022;25:246–55.
[11] Toth MJ, Fishman PS, Poehlman ET. Free-living daily energy expenditure in patients with Parkinson's disease. Neurology 1997;48:88–91.
[12] Diano S, Farr SA, Benoit SC, McNay EC, da Silva I, Horvath B, et al. Ghrelin controls hippocampal spine synapse density and memory performance. Nat Neurosci 2006;9:381–8.
[13] During MJ, Cao L, Zuzga DS, Francis JS, Fitzsimons HL, Jiao X, et al. Glucagon-like peptide-1 receptor is involved in learning and neuroprotection. Nat Med 2003;9:1173–9.
[14] de la Monte SM, Wands JR. Alzheimer's disease is type 3 diabetes-evidence reviewed. J Diabetes Sci Technol 2008;2:1101–13.
[15] Harvey J. Leptin regulation of neuronal excitability and cognitive function. Curr Opin Pharmacol 2007;7:643–7.
[16] Karra E, Chandarana K, Batterham RL. The role of peptide YY in appetite regulation and obesity. J Physiol 2009;587:19–25.
[17] Erbil D, Eren CY, Demirel C, Küçüker MU, Solaroğlu I, Eser HY. GLP-1's role in neuroprotection: a systematic review. Brain Inj 2019;33:734–819.
[18] Ge L, Liu S, Rubin L, Lazarovici P, Zheng W. Research progress on neuroprotection of insulin-like growth factor-1 towards glutamate-induced neurotoxicity. Cells 2022;11.
[19] Shi X, Zheng J, Ma J, Wang Z, Sun W, Li M, et al. Insulin-like growth factor in Parkinson's disease is related to nonmotor symptoms and the volume of specific brain areas. Neurosci Lett 2022;783:136735.
[20] Politis M, Wu K, Molloy S, P GB, Chaudhuri KR, Piccini P. Parkinson's disease symptoms: the patient's perspective. Mov Disord 2010;25:1646–51.
[21] Chen H, Zhang SM, Hernán MA, Willett WC, Ascherio A. Weight loss in Parkinson's disease. Ann Neurol 2003;53:676–9.
[22] Stunkard AJ, Messick S. The three-factor eating questionnaire to measure dietary restraint, disinhibition and hunger. J Psychosom Res 1985;29:71–83.
[23] Yesavage JA, Brink TL, Rose TL, Lum O, Huang V, Adey M, et al. Development and validation of a geriatric depression screening scale: a preliminary report. J Psychiatr Res 1982;17:37–49.
[24] Dalrymple-Alford JC, MacAskill MR, Nakas CT, Livingston L, Graham C, Crucian GP, et al. The MoCA: well-suited screen for cognitive impairment in Parkinson disease. Neurology 2010;75:1717–25.
[25] Martinez-Martin P, Rodriguez-Blazquez C, Alvarez-Sanchez M, Arakaki T, Bergareche-Yarza A, Chade A, et al. Expanded and independent validation of the movement disorder society-unified Parkinson's disease rating scale (MDS-UPDRS). J Neurol 2013;260:228–36.
[26] Seino Y, Fukushima M, Yabe D. GIP and GLP-1, the two incretin hormones: similarities and differences. J Diabetes Investig. 2010;1:8–23.
[27] De Silva A, Bloom SR. Gut hormones and appetite control: a focus on PYY and GLP-1 as therapeutic targets in obesity. Gut Liver 2012;6:10–20.
[28] Adrian TE, Ferri GL, Bacarese-Hamilton AJ, Fuessl HS, Polak JM, Bloom SR. Human distribution and release of a putative new gut hormone, peptide YY. Gastroenterology 1985;89:1070–7.
[29] Yu J, Min D, Bai Y, Qu L, Zou T, Wang S. Electroacupuncture alleviates Parkinson disease and regulates the expression of brain-gut peptides. Exp Anim 2020;69:448–60.
[30] Hellström PM, Näslund E. Interactions between gastric emptying and satiety, with special reference to glucagon-like peptide-1. Physiol Behav 2001;74:735–41.
[31] Nauck MA, Vardarli I, Deacon CF, Holst JJ, Meier JJ. Secretion of glucagon-like peptide-1 (GLP-1) in type 2 diabetes: what is up, what is down? Diabetologia 2011;54:10–8.
[32] Brunton S. GLP-1 receptor agonists vs. DPP-4 inhibitors for type 2 diabetes: is one approach more successful or preferable than the other? Int J Clin Pract 2014;68:557–67.
[33] Alagiakrishnan K, Sankaralingam S, Ghosh M, Mereu L, Senior P. Antidiabetic drugs and their potential role in treating mild cognitive impairment and Alzheimer's disease. Discov Med 2013;16:277–86.
[34] Meissner WG, Remy P, Giordana C, Maltête D, Derkinderen P, Houéto JL, et al. Trial of lixisenatide in early Parkinson's disease. N Engl J Med 2024;390:1176–85.
[35] Trapp S, Brierley DI. Brain GLP-1 and the regulation of food intake: GLP-1 action in the brain and its implications for GLP-1 receptor agonists in obesity treatment. Br J Pharmacol 2022;179:557–70.
[36] Friedman JM, Halaas JL. Leptin and the regulation of body weight in mammals. Nature 1998;395:763–70.

[37] Chan JL, Heist K, DePaoli AM, Veldhuis JD, Mantzoros CS. The role of falling leptin levels in the neuroendocrine and metabolic adaptation to short-term starvation in healthy men. J Clin Invest 2003;111:1409–21.
[38] Lima DP, de Almeida SB, Bonfadini JC, de Luna JRG, de Alencar MS, Pinheiro-Neto EB, et al. Clinical correlates of sarcopenia and falls in Parkinson's disease. PLoS One 2020;15:e0227238.
[39] Baert F, Matthys C, Mellaerts R, Lemaître D, Vlaemynck G, Foulon V. Dietary intake of Parkinson's disease patients. Front Nutr 2020;7.
[40] Cereda E, Barichella M, Pezzoli G. Controlled-protein dietary regimens for Parkinson's disease. Nutr Neurosci 2010;13:29–32.
[41] Boelens Keun JT, Arnoldussen IA, Vriend C, van de Rest O. Dietary approaches to improve efficacy and control side effects of levodopa therapy in Parkinson's disease: a systematic review. Adv Nutr 2021;12:2265–87.
[42] Knight E, Geetha T, Burnett D, Babu JR. The role of diet and dietary patterns in Parkinson's disease. Nutrients 2022;14:4472.
[43] Coelho-Junior HJ, Calvani R, Azzolino D, Picca A, Tosato M, Landi F, et al. Protein intake and sarcopenia in older adults: a systematic review and meta-analysis. Int J Environ Res Publ Health 2022;19.
[44] Zilli Canedo Silva M, Carol Fritzen N, de Oliveira M, Paes da Silva M, Rasmussen Petterle R, Teive HA, et al. Protein intake, nitrogen balance and nutritional status in patients with Parkinson's disease; time for a change? Nutr Hosp 2015;31:2764–70.
[45] Flint A, Raben A, Blundell JE, Astrup A. Reproducibility, power and validity of visual analogue scales in assessment of appetite sensations in single test meal studies. Int J Obes Relat Metab Disord 2000;24:38–48.
[46] Delikanaki-Skaribas E, Trail M, Wong WW, Lai EC. Daily energy expenditure, physical activity, and weight loss in Parkinson's disease patients. Mov Disord 2009;24:667–71.
[47] Logroscino G, Marder K, Cote L, Tang MX, Shea S, Mayeux R. Dietary lipids and antioxidants in Parkinson's disease: a population-based, case-control study. Ann Neurol 1996;39:89–94.
[48] Bailey RL. Overview of dietary assessment methods for measuring intakes of foods, beverages, and dietary supplements in research studies. Curr Opin Biotechnol 2021;70:91–6.
[49] Rolls BJ, Morris EL, Roe LS. Portion size of food affects energy intake in normal-weight and overweight men and women. Am J Clin Nutr 2002;76:1207–13.
[50] Sauerbier A, Jenner P, Todorova A, Chaudhuri KR. Non motor subtypes and Parkinson's disease. Parkinsonism Relat Disorders 2016;22(Suppl 1):S41–6.