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Original/*Otros*

Protein intake, nitrogen balance and nutritional status in patients with Parkinson's disease; time for a change?

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Abstract

Objective: **to evaluate protein intake, nitrogen balance and nutritional status of clinically stable patients with Parkinson's disease (PD).**

Methods: **a cross-sectional study of PD patients Hoehn-Yahr scale stage 1-3 and subjects with no neurologic disease (controls) matched for age and gender. All participants underwent a diet history interview, anthropometric measurements, bioelectrical impedance and food record over three non-consecutive days, including a weekend. A 24-hour urine collection and fasting venous blood sampling were collected from the participants for evaluation of creatinine clearance, creatinine height index and the nitrogen balance.**

Results: **the mean age of PD patients was 58.9 ± 12.8 year compared to 54.7 ± 12.6 year of the controls, P = 0.34. One third of PD group had symptoms of dysphagia and ingested less water and fibers when compared to controls. Calf circumference was small in PD group (35.5 ± 2.8 vs. 38.4 ± 3.5 cm, P = 0.012). Intake of nitrogen was significantly lower and nitrogen balance was negative in PD patients (-1.8 ± 3.9 vs. 1.1 ± 4.2 controls, P = 0.06). The antioxidants folate and vitamin E were consumed in small amounts in both groups, although significantly less in PD patients (P = 0.04 and 0.03, respectively).**

Discussion: **daily intakes of protein of approximately 1.1 g/kg by clinically stable PD patients may not be enough to ensure a neutral calorie-nitrogen balance and muscle tissue conservation. Larger studies are necessary to provide a more comprehensive picture of PD patients' metabolic status.**

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Key words: *Parkinson Disease. Nutritional status. Nitrogen balance.*

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INGESTIÓN PROTEICA, BALANCE NITROGENADO Y ESTADO NUTRICIONAL EN PACIENTES CON ENFERMEDAD DE PARKINSON; ¿TIEMPO PARA CAMBIOS?

Resumen

Objetivo: **evaluar ingestión proteica, balance nitrogenado y estado nutricional de pacientes con enfermedad de Parkinson (EP) clínicamente estables.**

Métodos: **estudio transversal de pacientes con EP en los niveles 1-3 según la escala de Hoehn-Yahr e individuos sin enfermedad neurológica (controles), pareados por edad y género. Todos los participantes fueron sometidos a una entrevista de la historia nutricional, antropometría, impedancia eléctrica y registro alimentario de 3 días consecutivos, incluyendo un fin de semana. Fueron colectados sangre venosa en ayuno y orina de 24 horas para evaluación de la depuración de la creatinina, índice creatinina-altura y balance nitrogenado.**

Resultados: **el promedio de edad en pacientes con EP fue 58,9 ± 12,8 años en comparación con 54,7 ± 12,6 años de los controles, p = 0,345. Un tercio del grupo EP tuvo síntomas de disfagia, con menor ingestión de agua y fibras, comparados a los controles. La circunferencia de la pantorrilla fue menor en grupo EP (35,5 ± 2,8 vs. 38,4 ± 3,5 cm, p = 0,012). La ingestión de nitrógeno fue significativamente menor y el balance de nitrógeno fue negativo en grupo EP (-1,8 ± 3,9 vs. 1,1 ± 4,2 controles, p = 0,064). Los antioxidantes folato y vitamina E fueron consumidos en pequeñas cantidades en ambos grupos, aunque significativamente menor en los pacientes con EP (p = 0,042 y 0,031, respectivamente).**

Discusión: **la ingestión proteica diaria de aproximadamente 1,1 g/kg en pacientes clínicamente estables con EP puede no ser suficiente para garantizar un balance neutro de calorías-nitrógeno, así como para mantener la masa muscular. Serán necesarios mayores estudios que produzcan una imagen más completa del estado metabólico de los pacientes con Parkinson.**

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Palabras clave: *Enfermedad de Parkinson. Estado nutricional. Balance nitrogenado.*

Abbreviations

PD: Parkinson Disease.
HY: Hoehn and Yahr scale.
EAT-10: Eating Assessment Tool.
FOIS: Functional Oral Intake Scale.
BMI: Body Mass Index.
CC: Calf Circumference.
WHO: World Health Organization.
SMI: Skeletal Muscle Index.
BF: Body Fat.
BIA: Bioelectrical Impedance.
DRI: Dietary Reference Intakes.
EAR: Estimated Average Requirement.
AI: Adequate Intake.
NB: Nitrogen Balance.
CHI: Creatinine Height Index.
NAA: Neutral Aromatic Amino Acids.
RDA: Recommended Dietary Allowances.

Introduction

Parkinson's disease (PD) is recognized as the second most common neurodegenerative disorder after Alzheimer's disease and affects 1% of the population worldwide after the age of 65 years, with an incidence of 10 to 14 cases per 100,000 per year. PD results mainly from progressive degeneration of dopaminergic neurons in the substantia nigra and other monoaminergic cell groups in the brainstem[1].

It causes motor dysfunctions, such as bradykinesia, resting tremor, rigidity and postural instability, but also affects autonomic functions and cognition[2]. The treatment aims to increase dopamine levels and alleviate the symptoms. For this purpose, drugs as levodopa, for example, are commonly used[3].

Nutritional status can be compromised in patients with PD[1], often leading to weight loss. Low dietary intake due to dysphagia and anorexia, reduced absorption by slow gastric emptying and increased energy expenditure by high muscle activity has been suggested as possible weight loss mechanisms[4].

Adequate nutrition plays an important role in preventing complications and malnutrition in PD. In addition, it is important as a determinant of treatment response, since the intake of large quantities of proteins, especially animal proteins can compete with intestinal absorption of levodopa and reduce its absorption and effectiveness[5]. On the other hand, low consumption can lead to changes in nutritional status.

Thus, the aim of this study was to evaluate the protein intake, nitrogen balance and nutritional status of patients with Parkinson's disease.

Methods

This was a cross-sectional, observational study involving selected patients with primary PD attending an outpatient clinic for Movement Disorders from a tertiary, university-affiliated hospital. All patients were under chronic levodopa therapy and were classified as grade 1 to 3 from Hoehn and Yahr scale (HY).

Exclusion criteria were associated neurological disease, use of diuretics, physical limitations to the anthropometric measurements, and illiterate patients without caregivers to assist in food consumption notes. A control group, matched for age and gender, with no neurologic disease was recruited among patients in Internal Medicine Outpatient Clinic at the same institution.

A detailed nutritional history was performed and patients were asked about comorbidities; bowel habits, being considered constipated individuals with less than three bowel movements per week; usual fluid intake; cough during meals; dysphagia symptoms as evaluated by the Eating Assessment Tool (EAT-10)[6], and safety and adequate oral intake by Functional Oral Intake Scale - FOIS[7].

In all patients, weight, height, body mass index (BMI), calf circumference (CC) were measured using an electronic scale, a stadiometer and an inelastic tape measure, respectively, according to the methods recommended by the World Health Organization (WHO)[8]. Analysis of body composition as skeletal muscle index (SMI)[9] and body fat (BF)[10] was performed by bioelectrical impedance (BIA) using an RJL Systems Quantum-101Q® device (Michigan, MI).

The habitual energy and nutrient intakes were determined by a food record over three non-consecutive days, including a weekend. The subjects collected a 24-hour urine sample during the last day of the recording period. To minimize the loss of urine, they were given detailed oral and written instructions concerning the collection. The analysis and calculation of food records were made through a Microsoft Excel spreadsheet (2010), using serving sizes and food composition tables[11].

Adequacy of intake for all nutrients analyzed was provided by the Dietary Reference Intakes (DRI) for age and sex. The estimated average requirement (EAR) values were considered, and when unavailable, the adequate intake (AI) values were used[12].

Blood and urine creatinine were measured by alkaline picrate reaction, and we calculated the creatinine clearance. Urea was measured after its hydrolysis by urease, and protein by biuret method. Nitrogen balance (NB) was calculated based on nitrogen intake and on total urinary nitrogen in a 24-hour urine collection[13] and creatinine height index (CHI) by the ratio of 24-hour urine creatinine x 100 and ideal urinary creatinine according to height, age and sex[14].

Analyses were performed by R version 3.0.2 software. (R Development Core Team, 2013). The Shapiro-Wilk test was used to assess the normality of the data, which were expressed as mean and standard deviation, or as median, minimum and maximum value. To test the statistical differences between the groups

we used the parametric Student's t test and the non-parametric Wilcoxon Mann-Whitney test. To assess relationships between variables, Pearson's correlations or Spearman's for non-normal distributions were used. All statistical tests were two tailed, with a significance level of $p < 0.05$.

The local ethics committee approved the study, and written informed consent was obtained from each subject.

Results

A total of 17 patients with PD were investigated. Their average age was 58.9±12.8 year, and 53% (9/17) were males. Eight PD patients were classified as grade 1, eight as grade 2 and one patient as grade 3 from HY scale. The control group comprised 17 individuals with an average age of 54.7±12.6 year, 53% of whom were also male. Baseline demographic, anthropometric and biochemical data of both groups are shown in table I. The BMI of the control group was higher (median 27.9 vs. 26.3, p<0.058) than the PD group, but both groups are classified as overweight, as defined by WHO. The mean of CC was the only anthropometric measure significantly different between the groups, with control group having higher values when compared to PD disease patients.

PD group had a mean protein intake of 1.1±0.3 g/kg compared to 1.2±0.5 g/kg of the controls, p=0.31. We also found that PD patients ingested significantly less nitrogen when compared to the control group (Fig. 1) and their nitrogen balance was negative (-1.8±3.9 vs. 1.1±4.2 g/day, p<0.06). No correlation was found between CC or SMI and protein and energy intake, NB and CHI (p=NS).

Creatinine clearance was similar in both groups, 92.5±26.9 mL/min for PD patients and 91.3±29.2 mL/min for controls, p=0.91. Diabetes mellitus (2/17, 11.8% in PD group and 3/17, 17.7 in control group, p=NS) and high blood pressure (7/17, 41.2% in PD group and 6/17, 35.3% in the control group, p=NS) were the most common comorbidities, evenly distributed between the groups.

Nonmotor complications were assessed in both groups. Dysphagia symptoms were present in five (30%) patients with PD classified as level six according to FOIS scale. Similar results were found by the self-assessment questionnaire to identify the risk of dysphagia, EAT-10, 35.3% (n=6) of patients were classified as risk. None of the subjects of the control group referred symptoms of dysphagia or had it detected by EAT-10 (p<0.04 vs. PD). Two patients with PD complained of cough during meals compared to one subject from the control group. Constipation was present in very few subjects in both groups (two in PD group and one in controls, p=NS).

As depicted in table II, energy intake, consumption of carbohydrate, protein, and different types of fat were similar among the groups. Relative to control

Table I
Baseline demographic, anthropometric and biochemical data of both groups

	PD (n=17)	*Controls (n=17)*	*p value*
Age (years)	58.9 ± 12.8	54.7 ± 12.6	0.35
Gender			
Male, n (%)	9 (52,9)	9 (52,9)	
Female, n (%)	8 (47,1)	8 (47,1)	
Body weight (kg)	70.3 ± 12.0	75.4 ± 13.1	0.25
Height (m)	1.7 ± 0.1	1.6 ± 0.1	0.08
BMI (kg/m²)*	26.3 (20.5-30.6)	27.9 (20.0-38.0)	0.058
CC (cm)	35.5 ± 2.8	38.4 ± 3.5	0.012
BIA			
SMI (kg/m²)	8.9 ± 1.7	9.8 ± 1.6	0.15
BF (%)	28.1 ± 8.2	32.0 ± 10.7	0.24
NB (g/day)**	- 1.8 ± 3.9	1.1 ± 4.2	0.06
Nitrogen intake (g)	10.6 ± 4.4	14.4 ± 4.1	0.019
Nitrogen excretion (g)	12.4 ± 3.3	13.3 ± 3.7	0.47
CHI (%)**	114.9 ± 29.7	121.3 ± 28.2	0.545

Values are presented as mean ± SD
*BMI: Values are presented as median (minimum-maximum)
**NB: n=15; CHI PD: n=16; CHI Controls: n=15

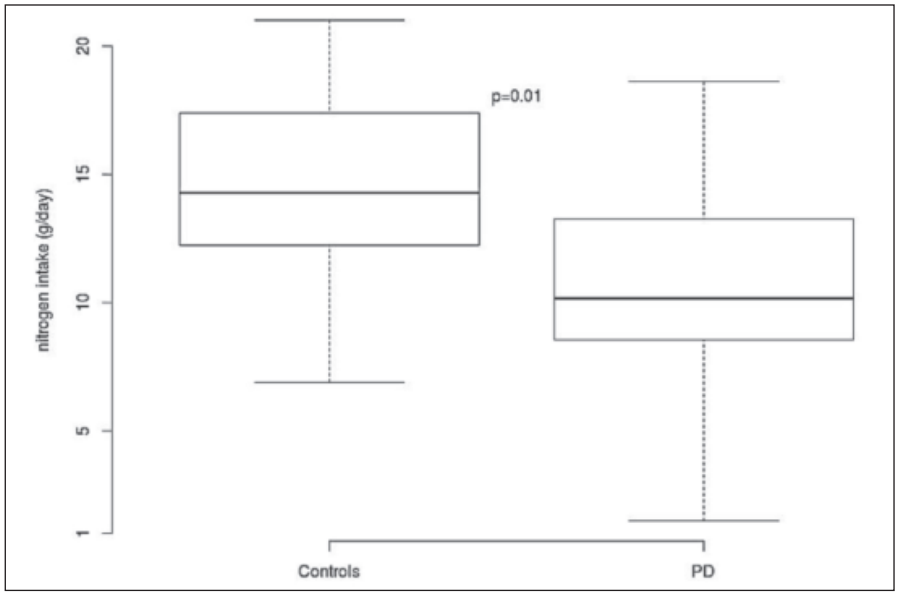

Fig. 1.—Nitrogen intake (g/day) of both groups.

Table II
Macronutrient intake, water and fiber per day of both groups

	PD (n=17)	*Controls (n=17)*	*p value*
Energy (kcal)*	2018.6 (1248.9-2683.7)	2152.8 (991.3-4672.2)	0.24
Carbohydrate (g)	275.7 (104.7-401.1)	262.6 (139.1-625.0)	0.97
Protein (g)*	73.8 (42.3-118.4)	92.8 (44.1-133.0)	0.10
Fat (%)	30.9 (21.1-52.0)	28.4 (19.3-43.6)	0.22
Cholesterol (mg)	238.0 (126.1-647.9)	277.9 (102.0-627.1)	0.47
Saturated fatty acids (%)*	11.5 (8.4-18.2)	10.4 (7.6-17.2)	0.20
Mono unsaturated fatty acids (%)	10.2 (6.9-19.7)	10.6 (7.1-17.5)	0.71
Poly unsaturated fatty acids (%)*	5.3 (3.6-9.3)	5.2 (3.3-7.7)	0.84
Trans fat (%)	1.7 (0.8-4.2)	1.3 (0.6-2.8)	0.11
Fiber (g)	16.2 (6.9-35.6)	24.5 (10.4-90.6)	0.013
Water (mL)	800 (200-2000)	1800 (200-4000)	0.019
Energy (kcal/kg)	30.9 (18.3-44.6)	27.4 (14.5-62.5)	0.74
Protein (g/kg)	1.1 (0.7-1.8)	1.2 (0.6-2.3)	0.31

Values are presented as median (minimum-maximum)
*Test t for parametric data.

group, PD patients ingested significantly less water (median 800 ml vs. 1800 ml, p=0.019)) and total fiber (16.2 vs. 24.5 grams, p=0.013) per day.

We extensively evaluated the intake of minerals and vitamins consumption in both groups. There were small differences (albeit statistically significant) in the intake of folate and vitamin E between the groups, with higher consumption in the control group, as demonstrated in table III. Adequacy of intake (in percentage of DRI) for some nutrients analyzed in this work is shown in figure 2.

Discussion

The investigation showed that clinically stable, grade 1 to 3 HY PD patients doesn't had adequate daily calorie and protein intake to meet their metabolic needs and had negative NB. Consequently, they had low muscle mass as assessed by CC and potentially reduced energy availability for daily life. One third of them had symptoms of dysphagia and ingested less water and fibers when compared to controls. In addition, two import antioxidants (folate and vitamin E) were consumed in small amounts.

Table III
Micronutrient intake, water and fiber per day of both groups

	PD (n=17)	*Controls (n=17)*	*p value*
Calcium (mg)	623.2 (279.5-1229.4)	816.2 (413.8-1825.2)	0.30
Magnesium (mg)	223.8 (97.9-343.1)	267.9 (64.1-926.8)	0.08
Manganese (mg)	2.1 (1.5-20.0)	3.0 (0.8-8.8)	0.17
Phosphorus (mg)	987.1 (530.3-1660.9)	1276.4 (535.1-2983.4)	0.24
Iron (mg)	9.4 (5.3-18.6)	11.1 (4.0-32.8)	0.08
Sodium (mg)	2980.5 (1385.5-4432.5)	3691.3 (1158.4-8584.8)	0.17
Potassium (mg)	2289.2 (1028.0-3858.1)	2908.3 (1254.4-8273.4)	0.11
Copper (mg)	0.9 (0.6-10.9)	1.1 (0.4-5.5)	0.26
Zinc (mg)	9.6 (5.1-17.4)	11.2 (4.1-27.7)	0.058
Selenium (mcg)	79.1 (40.6-120.2)	94.6 (32.9-206.6)	0.23
Vitamin A (mcg)	487.5 (157.9-6882.5)	676.3 (202.2-6320.1)	0.29
Thiamin (mg)	1.4 (0.6-2.2)	1.4 (0.5-4.1)	0.89
Riboflavin (mg)*	2.0 (1.0-4.4)	2.2 (0.8-3.5)	0.73
Niacin (mg)	16.2 (7.3-31.2)	16.9 (5.0-45.1)	0.51
Vitamin B6 (mg)	1.6 (0.8-3.7)	1.9 (0.7-3.7)	0.41
Vitamin B12 (mcg)	3.3 (2.0-51.7)	5.0 (1.4-26.5)	0.14
Folate (mcg)	224.8 (106.2-541.7)	317.5 (99.4-1255.2)	0.042
Vitamin D (mcg)	4.1 (1.4-7.9)	4.2 (1.6-18.4)	0.76
Vitamin E (mg)	3.6 (3.1-6.4)	5.1 (2.6-21.1)	0.031
Vitamin C (mg)	85.9 (8.5-662.4)	85.8 (18.9-610.6)	0.58

Values are presented as median (minimum-maximum)
*Test t for parametric data.

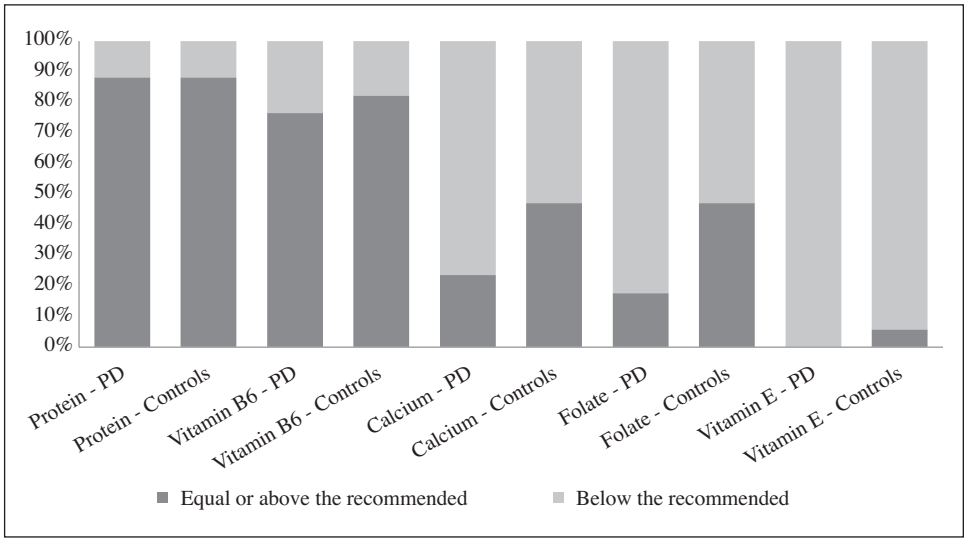

Fig. 2.—Adequacy of intake (%) for some nutrients per day of both groups.

Patients with chronic neurological diseases are in increase risk of malnutrition by multiple factors related to nutrient ingestion, abnormalities in the energy expenditure, changes in eating behavior, and gastrointestinal changes[4].

Whereas bradykinesia, rigidity, tremor, and postural instability result in disability, nonmotor complications in PD may be equal or greater significance in some patients and can significantly change the nutritional status[1].

Autonomic dysfunction is one of these complications, which may present as gastrointestinal, urinary, and sexual disturbances. In effect, one third of our patients had presented advanced dysphagia. Some au-

thors have proposed that this condition can affect over 80% of individuals, reflecting the underlying motor impairments and the extent of the disease's progression. These dysphagia-related impairments have a direct influence on the nutritional and health status of the patients, and are associated with increased morbidity and mortality[15].

Levodopa is the most effective drug for the symptomatic treatment of PD[3]. Unfortunately, the neutral aromatic amino acids (NAA) contained in dietary proteins may compete with this drug for intestinal absorption and transport across the blood-brain barrier, thus limiting its efficacy and being responsible for the occurrence of motor fluctuations[16]. A reduction of protein intake to 0.75-0.8 g/kg body weight/day has been recommended in PD with protein redistribution, as shifting protein intake to the evening has showed to ameliorate the response to levodopa. However, some authors have suggested that in elderly patients protein restriction may lead to a lasting negative nitrogen balance, and even in younger patients the supply of certain minerals and vitamins may become too low or marginally adequate[17]. Furthermore, the restriction of protein intake seems to be effective only in a small group of patients[18].

In the present study, PD patients had a mean intake of 1.1±0.3 g/kg of protein (vs. 1.2±0.5 g/kg from controls, p=0.308) and ingested 10.6±4.4 g/day of nitrogen compared to 14.4±4.1 of the control group, P=0.019. Similar results have been found in more recent studies[3]. Nitrogen balance was negative, although the difference between the groups did not reach statistical significance (Table I). Body proteins are in a constant state of flux, with degradation and synthesis constantly going on. When necessary, muscle protein becomes a source of energy, resulting in a negative nitrogen balance.

Calf circumference correlates positively with muscle mass and values lower than 31 cm has been associated with disability[19]. In the current work, CC was significantly lower in the PD patients compared to the control group (Table I). In other study, CC showed no significant difference, and the control subjects had lower values[20].

However, age-related changes in fat deposits and loss of skin elasticity can lead to imprecise measurements in older people. BIA could be used for sarcopenia screening. Our data demonstrated similar values of muscle mass index as assessed by BIA in both groups (Table I).

While maintaining nitrogen balance is critical for health, there are some suggestions that Recommended Dietary Allowances (RDA) may not be the right amount of protein needed to promote optimal health in healthy individuals. To achieve that, more protein is needed, and recent studies suggest that athletes, active people, and older individuals require even more[21].

Our investigation offers some evidence that spontaneous nutrition of clinically stable PD patients, likewise observed in other chronic diseases[22] may not balance for the various catabolic factors that can be present and that a recommended "normal" protein intake is not synonymous with an "adequate" protein intake. Although excessive protein intake remains a concern in subjects with pre-existing renal disease, the literature lacks significant research demonstrating a link between protein intake and the initiation or progression of renal disease in healthy individuals[23]. As showed in the results section, glomerular filtration rate as estimated by the creatinine clearance was normal for both groups.

Finally, some data suggest that is not necessary to limit protein intake in PD to achieve stable levels of levodopa and NAA. By the opposite, in susceptible patients, consumption of meals containing high carbohydrate, but lacking enough protein, can cause signs' of levodopa toxicity (dyskinesias), probably because too much drug suddenly enters the brain[24].

A large systematic review and meta-analysis found that dietary intake of vitamin E protects against PD. This protective influence was seen with both moderate intake (relative risk 0.81, 95% CI 0.67-0.98) and high intake (0.78, 0.57-1.06) of vitamin E. The authors concludes that although the results requires confirmation in randomized controlled trials, dietary vitamin E may have a neuroprotective effect attenuating the risk of PD[25]. In our work, both groups had a very low intake of vitamin E (median 3.6 vs. 5.1 in the control group, p<0.031), well below the EAR of 12 mg. These intake estimates might be low, however, because the amounts and types of fat added during cooking are often unknown and not accounted for. Additionally, in people who already have PD, high-dose vitamin E was not able to slow disease's progression[26].

There is conflicting evidence regarding the usefulness of folic acid in PD. In patients with low or low-normal folate levels, levodopa administration is associated with increases in homocysteine[27]. This aminoacid is associated with cardiovascular risks, neuropsychiatric illness, and increased fractures in elderly persons. As depicted in table III our PD patients had an estimated intake of folic acid of 224.8 μg/day in median, below the EAR of 320 μg/day.

In our opinion, the main limitation of this study was the sample size of our population. The small sample size limits generalizability, so larger-scale studies are urgently needed. Nonetheless, this sample is probably an accurate representation of PD patients presenting to Movement Disorders outpatient clinics. Second, a significant amount of the clinical information was based on interviews with patients and their caregivers, which could have resulted in recall bias. We are also aware that because of its cross-sectional design, this study does not allow to establish any cause-effect relationships.

In conclusion, we believe that the present work has implications for clinical practice. Daily intakes of protein of approximately 1.1 g/kg by clinically stable, predomi-

nantly 1-2 HY scale, PD patients may not be sufficient to ensure a neutral calorie nitrogen balance and muscle tissue conservation. As advised in other chronic diseases[22], this study emphasizes the importance to estimate nitrogen balance and not only macronutrient intakes. Therefore, larger studies involving more PD patients and matched controls may help in providing a more comprehensive picture of the patients' metabolic status.

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