Dietary Intakes and Plasma Polyunsaturated Fatty Acid Levels in Parkinson's Disease

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Abstract

The study aims to determine the correlation between dietary intakes and plasma concentrations of PUFA and their associations with clinical severities in PD. We designed a case-control study to assess dietary fat intakes and disease severity in 38 PD patients and 33 healthy volunteers. Plasma levels of five PUFAs including α -linolenic acid (ALA), eicosapentaenoic acid, docosahexaenoic acid, linoleic acid (LA), and arachidonic acid (AA) were measured using gas chromatography.

No differences were observed in dietary total energy and lipid intakes including PUFAs between two groups. PD patients had lower plasma levels of ALA, LA, and AA than controls. The associations between dietary intake and plasma concentrations of PUFAs were insignificant, whereas the association between dietary intake and plasma concentration of AA was exceptionally significant in controls. Plasma levels of ALA and LA were inversely associated with motor rating scores in PD patients, while that of AA was positively associated with non-motor symptoms.

Plasma levels of ALA, LA, and AA were lower in PD patients than those in healthy controls, suggesting absorption problems in PD or expedited utilization of PUFAs. Contradictory relations on motor and non-motor symptoms imply conflicting clinical effects of PUFAs, raising questions about the usefulness of PUFA supplementation.

Introduction

Parkinson's disease (PD) is the second most common neurodegenerative disease affecting approximately 1% of people aged 65 years or more. Environmental factors are important in the pathogenesis of PD, specifically in patients older than 50 years¹. Daily food intake is consistently studied as an important environmental factor².

Regarding fatty acid, the role of polyunsaturated fatty acid (PUFA) has been widely studied. In animal studies, omega-3 (ω -3) PUFA has the following beneficial effects: it protects nigral dopamine neurons, mitigates motor severity, or delays the development of levodopa-induced dyskinesia^{3,4}. On the contrary, abundant PUFA in neural plasma membranes could be sources of oxygen radicals through lipid peroxidation⁵ and could promote α -synuclein (α Syn) oligomerization with further aggregation according to *in vitro* and *in vivo* mouse models^{6,7}. Clinical studies assessing the associations between PUFA intake and PD risk also remained controversial⁸⁻¹¹, while direct analyses of lipid metabolites showed decreased PUFA level in PD^{12,13}. Although a few clinical trials using ω -3 PUFA supplementations reported clinical benefits of PUFA, the number of patients was small or vitamin E was co-administered in these trials^{14,15}.

Previously, either food questionnaire or direct measurement of PUFA was adapted to investigate the role of PUFA in PD, which was insufficient to reveal the association between dietary habit and plasma PUFA level. In this study, we simultaneously examined the dietary fat intake and plasma concentration of PUFA, allowing us to determine the factors associated with plasma PUFA.

Results

Demographic factors, co-morbidity, and other lipid levels were previously described¹⁶, which were not different between PD patients and controls, while WCS and K-NMSS score were significantly higher in PD patients than those in controls (**Table 1**).

There were no significant differences in dietary intakes including total energy, total fat, cholesterol, and total fatty acids, saturated fatty acids, monounsaturated fatty acids, and PUFA between PD patients and controls (**Table 2**). The ratio of ω -6 to ω -3 PUFA (ω -6/ ω -3 ratio) based on dietary intakes was not different between the two groups.

The plasma levels of α -linolenic acid (ALA, C18:3n3) ($p=0.017$), linoleic acid (LA, C18:2n6) ($p=0.003$), and arachidonic acid (AA, C20:4n6) ($p=0.024$) were lower in PD patients than those in controls (**Table 3** and **Figure 1**). The levels of eicosapentaenoic acid (EPA, C20:5n3) and docosahexaenoic acid (DHA, C22:6n3) were lower in PD patients compared to controls, but the difference between the two groups was insignificant. The ω -6/ ω -3 ratio in the plasma was insignificantly different between PD patients and controls. The plasma level of LA was lower in patients taking catechol-O-methyltransferase inhibitor than that in patients not taking catechol-O-methyltransferase inhibitor (211.8 ± 50.4 versus 269.2 ± 71.0 $\mu\text{g/mL}$, respectively, $p=0.025$ [**Supplementary Table S1**]).

There were no significant associations between dietary intakes and plasma levels of PUFA in PD patients (**Supplementary Figure S1**). In the control group, AA intake was associated with plasma concentrations ($\rho=0.424$, $p=0.016$).

The severity of motor symptoms (UPDRS III) was negatively associated with ALA and LA concentrations ($\rho=-0.318$, $p=0.052$ for ALA; $\rho=-0.380$, $p=0.018$ for LA) (**Table 3, Supplementary Table S2**). Plasma AA level was positively associated with UPDRS nonmotor scores (UPDRS I), specifically with depression item ($\rho=0.332$, $p=0.041$ for UPDRS I; $\rho=0.338$, $p=0.038$ for depression item). Associations between plasma levels of PUFA and disease duration, UPDRS II, Hoehn and Yahr stage, and total medication dose were not observed.

We set outliers as any measures that are less than 1.5 interquartile range (IQR) below the lower quartile or more than 1.5 IQR above the upper quartile. When outliers of both dietary intakes and plasma levels of PUFA were removed and analyzed, the comparison results and statistical significance did not change between PD patients and healthy controls (data not shown). However, the strength of association between diet-plasma PUFA measures was weakened in the control group, when outliers were excluded for analysis ($\rho=0.346$, $p=0.071$). The correlation between plasma PUFA concentration and clinical parameters also did not change, but the positive correlation between plasma AA level and UPDRS I was no longer statistically significant ($\rho=0.155$, $p=0.382$).

Discussion

In this study, we examined five essential PUFAs based on the subjects' history of dietary intakes and plasma levels in PD.

Previous epidemiological studies investigated the role of PUFAs on the risk of PD, showing controversial results^{8–11, 17}. A recent review summarized that the risk of PD was negatively associated with the intakes of PUFA, ω -3 PUFA, or ALA and ω -3/ ω -6 ratio, while it was positively associated with the intakes of AA and ω -6 PUFA¹⁸. In our study, diet history of PUFA intake and calculated ω -6/ ω -3 ratio were insignificantly different between PD patients and controls. Although we did not intend to assess the risk of PD associated with PUFAs, our findings were inconsistent with those of previous diet studies.

In this study, we recruited patients with established diagnosis of PD. Considering that the mean disease duration of PD patients was 4 years, food consumption behavior could be modified by seeking "healthier" foods after the diagnosis, blunting unhealthy pattern during preclinical or early stage of the disease. Food behavior change could be indirectly conjectured by a study showing that the larger portion of PD patients (76%) in Korea took complementary or alternative medicine than that in Western countries^{19,20}. Previously, changes in the pattern of food intakes before and after the diagnosis of PD are not fully studied, except the increased total amount of energy intakes after PD diagnosis²¹. Further studies are required to assess the influence of PD diagnosis on the change of the pattern of food intake.

Only a couple of studies directly measured plasma levels of PUFA^{12,13}. Plasma levels of PUFAs also decreased in our PD patients, while the levels of other lipids were not different between PD patients and controls (Tables 1 and 3)^{12,13}. Previous studies reported decreased PUFAs as a part of profiling serum metabolites and did not pay attention to diet history. The discrepancy between dietary intake and plasma concentrations of PUFA was unexpected and first reported in PD.

Absorption and utilization of PUFAs should be considered when assessing the association between plasma PUFAs and PD. First, PUFAs are absorbed in the small intestines; thus, small intestinal bacterial overgrowth (SIBO) can hinder PUFA absorption^{22,23}. SIBO was frequently reported in PD patients and had negative effects on clinical features²⁴. Inflammation or deranged osmolarity by the bacteria may hamper normal absorption^{22,24}. In this study, a difference in dietary intakes of PUFAs between PD patients and controls was not observed, and the positive association between dietary intakes and plasma levels of AA in the control group suggested that malabsorption was the cause of decreased PUFAs in PD. Second, PUFAs are utilized by neurons, and expedited utilization could be hypothesized in association with pathologic change of local milieu such as oxidative stress in PD. Fatty acid-binding protein (FABP) is a protein translocating PUFA from the extracellular space inside the neurons. In PD, it was reported that FABP expression was elevated in the substantia nigra (SN)²⁵. This upregulation is understandable because the SN is highly energy-demanding and resultantly vulnerable to oxidative stress, and PUFAs have protective mechanisms against oxidative stress.

However, previous studies reported different levels of PUFAs in the brain. In the SN, PUFA level decreased along with lipid peroxidation, engendering harmful effects on the neurons⁵. In other studies, levels of PUFAs increased in the frontal cortices of

patients with Lewy body disease such as PD, and PUFA was also associated with α Syn oligomerization⁶. Therefore, the effect of PUFAs on the neurons is double-edged, fulfilling the demand of endangered neurons under oxidative stress but threatening neurons by lipid peroxidation and α Syn oligomerization.

In clinical analyses, the plasma levels of PUFAs were negatively associated with the severity of motor symptoms, implying a beneficial effect of PUFAs. Previous studies using ω -3 PUFAs produced inconsistent results, whereas clinical studies using ω -6 PUFAs were not conducted because of the unfavorable results obtained regarding the association between ω -6 PUFAs and PD risk^{10,11,18}. In our study, both ω -3 (ALA) and ω -6 (LA) PUFAs had negative associations with parkinsonian motor symptoms, while another ω -6 (AA) had a positive association with the severity of nonmotor symptoms. Therefore, the clinical benefit of PUFAs on PD is not straightforward.

There are several limitations to be considered. First, since the present study is a cross-sectional case-control study on PD patients, it is difficult to draw the causal interferences of PUFA on PD. Second, obtaining diet history can be affected by non-standardized method. In this study, nutritionists interviewed all the participants using standard FFQ of which the reliability and validity was established^{26,27}. Finally, there is an issue related to the reliability of a single cross-sectional measurement of PUFA levels. In this study, to prevent possible dietary effect, we asked the participants to fast more than 12 hours before blood sampling. And we simultaneously measured the levels of non-PUFA lipid to ensure the reliability of PUFA measurement, which were not different between PD patients and controls. Although we did not repeat the measurement of PUFA levels, repeated measurement of PUFA levels over 2–3 years showed consistent results in women from Nurses' Health Studies²⁸.

In conclusion, the simultaneous assessment of food intake history and plasma PUFA is firstly done to show possible absorption problem in PD. Overconsumption of PUFAs by vulnerable neurons with both beneficial and detrimental effect in PD is also conceivable. Finally, conflicting associations between PUFAs and clinical symptoms raise questions about the benefit of PUFA supplementation in PD.

Methods

Subjects

Thirty-eight PD patients and 33 controls aged between 50 and 75 years were included. Patients were diagnosed with PD according to the United Kingdom Parkinson's Disease Society Brain Bank Clinical Diagnosis Criteria²⁹. The inclusion criterion was as follows: patients not receiving antibiotics, immune-related drugs, and vaccines (for 3 months, respectively), lipid-lowering drugs (for 1 month), and vitamin supplements, ω -3 fatty acids, prebiotics, and probiotics (for 2 weeks, respectively)¹⁶. The exclusion criterion was as follows: patients with secondary parkinsonism, other significant central nervous system diseases, malignancy within the last 3 years, and significant gastrointestinal disorders¹⁶. The study has been approved by local ethics committee (Institutional Review Boards of Kyung Hee University Hospital, # KHUH 2017-08-035) and all subjects provided written informed consents before inclusion in the study in accordance with The Code of Ethics of the World Medical Association (Declaration of Helsinki).

Clinical and Nutritional Evaluation

All subjects were interviewed by a trained interviewer, using a structured questionnaire to obtain information on demographics, height, weight, and medical history (disease duration and medications). We used a validated 138-item semiquantitative food frequency questionnaire (FFQ) to assess usual dietary intake over the past 12 months, which were selected based on commonly consumed foods using the Korea National Health and Nutrition Examination Survey²⁷. The dietary intake of each nutrient was calculated based on the subjects' response to the FFQ and the Korean Food Composition Table by the Korean Nutrition Society program CAN-Pro 4.0 (Nutritional Assessment Program 2011 Korean Nutrition Society, Seoul, Korea). The Unified Parkinson's Disease Rating Scale (UPDRS), Wexner constipation score (WCS), and Korean version of the non-motor symptom scale (K-NMSS) were used for the subjects' clinical evaluation. Levodopa-equivalent daily dose was calculated based on the previous reference³⁰.

Sample Collection and Plasma Lipid Analysis

Blood samples were collected in the morning after the subjects were required to fast over 12 hours. We measured the levels of cholesterol, triglycerides, high- and low-density lipoprotein, and PUFA including ALA, EPA, DHA, LA, and AA.

All blood samples were prepared in a nonadditive blood collecting tube by adding 1 mg/mL of ethylenediaminetetraacetic acid and 1 mg/mL of reduced glutathione. Plasma was separated from the whole blood by centrifugation at 3000 rpm for 10 minutes immediately. The plasma was treated with 10 µl/ml of butylated hydroxytoluene-methanol and stored at – 80°C.

For PUFA analysis, the samples were dissolved in methanol containing methyl heptadecanoate (3 g/L) as an internal standard. Acetyl chloride was added to the dissolved samples for acid-catalyzed esterification and transesterification, and incubated for 45 minutes. For neutralization, potassium carbonate solution (6% in water) was mixed gently to the samples with hexane and subsequently placed on ice for 30 minutes. After cooling, tubes were centrifuged for 10 minutes at 3000 rpm. The extracted lipids of the supernatant were dried under nitrogen gas and washed with hexane by solvent.

The solution was injected by pulsed split mode into an Agilent 7890B gas chromatograph with a flame ionization detector using Agilent DB-WAX capillary column (30 m × 0.25 µm × 0.25 µm). The inlet and detector temperatures were 250°C and 270°C, respectively, and nitrogen was used as a carrier gas at a rate of 1 mL/min. The concentration of long chain fatty acid was calculated using the peak height ratio method³¹.

Data and Statistical Analyses

We applied Student's *t*-test and Mann-Whitney *U*-test to compare the means of two independent continuous variables according to assumption of normal distribution. Categorical data were compared by Pearson's chi-squared test analysis. Spearman's rank correlation coefficient analysis was applied to determine bivariate correlation. The Statistical Package for the Social Sciences (SPSS) software version 25.0 (SPSS Inc., Chicago, IL, USA) was used for statistical analysis with *p* < 0.05 considered as statistically significant (two-tailed).

Declarations

Authors' Contributions

Study design and supervision: Y.L. and T.A.

Recruitment of study subjects: C.S. and T.A.

Acquisition of data: Y.S., H.R., and C.S.

Analysis and interpretation of data: D.Y., Y.L., Y.S., H.R., and T.A.

Drafting the article: D.Y. and T.A.

Revising the manuscript critically for important intellectual content and final approval of the version to be published: all authors

Competing interests

The authors declare no competing interests.

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Data availability

The datasets collected and analyzed for the current study are available from the corresponding author on reasonable request.

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Tables

Table 1. Subjects' demographic and clinical data and plasma lipid levels

	PD (n=38)	HC (n=33)	<i>p</i> -value
Age, yr	66 (6)	66 (6)	0.945
Male, n (%)	17 (45)	10 (30)	0.211 ^a
Hypertension, n (%)	12 (32)	12 (36)	0.802 ^a
Diabetes mellitus, n (%)	8 (21)	3 (9)	0.202 ^a
BMI, kg/m ²	23.8 (2.8)	23.1 (2.7)	0.253 ^b
WCS (0–30)	3 (4)	0 (0)	<0.001
K-NMSS (0–360)	9 (7)	3 (3)	<0.001
Disease duration, yr	4 (3)	-	
UPDRS I	2 (2)	-	
UPDRS II	6(4)	-	
UPDRS III	20 (8)	-	
Hoehn and Yahr	2 (1)	-	
LEDD, mg/d	608 (331)	-	
Total cholesterol, mg/dL	189 (33)	204 (41)	0.127
TG, mg/dL	123 (67)	135 (59)	0.278
LDL, mg/dL	123 (26)	133 (29)	0.160 ^b
HDL, mg/dL	52 (10)	52 (16)	0.858

Data are described as mean (standard deviation) or frequency

For group comparisons, the Mann-Whitney *U* test was used if not otherwise indicated

^aPearson's chi-squared test

^bStudent's *t*-test

The *p*-values marked in bold indicate significant differences between groups.

Abbreviations: PD, Parkinson's disease; HC, healthy control; BMI, body mass index; WCS, Wexner constipation score; K-NMSS, Korean non-motor symptoms scale; UPDRS, Unified Parkinson's Disease Rating Scale; LEDD, levodopa-equivalent daily dose; TG, triglyceride; LDL, low-density lipoprotein; HDL, high-density lipoprotein

Table 2. Dietary intake based on a food frequency questionnaire in Parkinson's disease

g	PD (n=38)	HC (n=33)	p-value
Total energy intake, kcal	1935.05 (634.77)	1938.19 (493.88)	0.917
Fat, g	49.78 (26.48)	46.72 (16.57)	0.963
Vegetable fat	25.95 (16.08)	26.74 (13.67)	0.572
Animal fat	23.83 (12.82)	19.98 (6.03)	0.105 ^a
Cholesterol, mg	343.82 (177.78)	358.11 (151.97)	0.489
Total FA, g	34.09 (18.73)	31.58 (11.71)	1.000
Saturated FA	12.57 (7.55)	10.51(3.39)	0.135 ^a
MUFA	14.82 (8.95)	13.49 (4.52)	0.963
PUFA	11.56 (7.81)	11.42 (5.17)	0.704
ALA (C18:3n3)	0.98 (0.70)	0.96 (0.46)	0.908
EPA (C20:5n3)	0.13 (0.12)	0.11 (0.07)	0.881
DHA (C22:6n3)	0.28 (0.28)	0.24 (0.16)	0.721
LA (C18:2n6)	9.51 (6.17)	9.56 (4.73)	0.747
AA (C20:4n6)	0.02 (0.01)	0.01 (0.01)	0.475
ω -6/ ω -3 ratio ^b	7.30 (1.65)	7.40 (1.57)	0.799 ^a

Data are described as mean (standard deviation)

For group comparisons, the Mann-Whitney *U* test was used if not otherwise indicated

^aStudent's *t*-test

^b ω -6/ ω -3 ratio = (LA+AA)/(ALA+EPA+DHA)

Abbreviations: PD, Parkinson's disease; HC, healthy control; FA, fatty acid; MUFA, monounsaturated FA; PUFA, polyunsaturated FA; ALA, alpha-linolenic acid; EPA, eicosapentaenoic acid; DHA, docosahexaenoic acid; LA, linoleic acid; AA, arachidonic acid

Table 3. Clinical association between plasma level of polyunsaturated fatty acid in Parkinson's disease

Plasma concentration (µg/mL)	ALA		EPA		DHA		LA		AA		ω-6/ω-3 ratio ^b	
	<i>p</i>		<i>p</i>		<i>p</i>		<i>p</i>		<i>p</i>		<i>p</i>	
PD	21.8 (1.7)	0.017	16.1 (1.2)	0.396	14.4 (1.0)	0.114	254.1 (70.4)	0.003^a	37.3 (2.0)	0.024	6.4 (2.5)	0.163 ^a
HC	29.0 (2.4)		19.8 (2.3)		18.0 (1.8)		305.6 (66.4)		46.4 (3.3)		6.4 (1.7)	
	<i>ρ</i>	<i>p</i>	<i>ρ</i>	<i>p</i>	<i>ρ</i>	<i>p</i>	<i>ρ</i>	<i>p</i>	<i>ρ</i>	<i>p</i>	<i>ρ</i>	<i>p</i>
Disease duration, yr	-0.249	0.132	-0.079	0.635	-0.121	0.471	-0.124	0.459	-0.061	0.714	0.121	0.501
WCS (0–30)	-0.017	0.921	0.065	0.700	0.120	0.472	0.187	0.261	0.111	0.507	0.044	0.807
K-NMSS (0–360)	-0.152	0.363	-0.189	0.255	-0.164	0.326	-0.024	0.885	0.091	0.587	0.183	0.309
UPDRS I	0.060	0.720	0.142	0.395	0.281	0.087	-0.057	0.736	0.332	0.041	-0.093	0.606
UPDRS II	-0.001	0.994	0.188	0.257	0.288	0.080	-0.147	0.377	0.118	0.480	-0.124	0.493
UPDRS III	-0.318	0.052	-0.196	0.239	-0.147	0.380	-0.380	0.018	-0.234	0.158	0.107	0.555
Hoehn and Yahr	0.033	0.846	0.121	0.469	0.128	0.445	-0.049	0.772	0.061	0.715	-0.062	0.730
LEDD, mg/d	-0.060	0.721	0.122	0.467	0.252	0.128	0.013	0.938	-0.010	0.954	-0.126	0.483

Data are described as mean (standard deviation); The *p*-values marked in bold indicate statistical significance.

For group comparisons, the Mann-Whitney *U* test was used if not otherwise indicated; ^aStudent's *t* test

^bω-6/ω-3 ratio = (LA+AA)/(ALA+EPA+DHA), *ρ*: Spearman's rank correlation coefficient

Abbreviations: PUFA, polyunsaturated fatty acid; ALA, alpha-linolenic acid; EPA, eicosapentaenoic acid; DHA, docosahexaenoic acid; LA, linoleic acid; AA, arachidonic acid; PD, Parkinson's disease; HC, healthy control; WCS, Wexner constipation score; K-NMSS, Korean nonmotor symptoms scale; UPDRS, Unified Parkinson's Disease Rating Scale; LEDD, levodopa-equivalent daily dose

Figures

Figure 1

Plasma polyunsaturated fatty acid levels in Parkinson's disease Abbreviations: ALA, alpha-linolenic acid; EPA, eicosapentaenoic acid; DHA, docosahexaenoic acid; LA, linoleic acid; AA, arachidonic acid

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