

RESEARCH ARTICLE

Low-Fat Versus Ketogenic Diet in Parkinson's Disease: A Pilot Randomized Controlled Trial

Matthew C.L. Phillips, MSc, FRACP,^{1*} Deborah K.J. Murtagh,² Linda J. Gilbertson, BLitComm, PGCert(Nursing),¹ Fredrik J.S. Asztely, PhD, FRACP^{1,3} and Christopher D.P. Lynch, MD, FRACP¹

¹Department of Neurology, Waikato Hospital, Hamilton, New Zealand

²Healthy Kitchen Christchurch Ltd, Hamilton, New Zealand

³Institute of Neuroscience and Physiology, University of Gothenburg, Gothenburg, Sweden

ABSTRACT: Background: Preliminary evidence suggests that diet manipulation may influence motor and nonmotor symptoms in PD, but conflict exists regarding the ideal fat to carbohydrate ratio.

Objectives: We designed a pilot randomized, controlled trial to compare the plausibility, safety, and efficacy of a low-fat, high-carbohydrate diet versus a ketogenic diet in a hospital clinic of PD patients.

Methods: We developed a protocol to support PD patients in a diet study and randomly assigned patients to a low-fat or ketogenic diet. Primary outcomes were within- and between-group changes in MDS-UPDRS Parts 1 to 4 over 8 weeks.

Results: We randomized 47 patients, of which 44 commenced the diets and 38 completed the study (86% completion rate for patients commencing the diets). The ketogenic diet group maintained physiological ketosis. Both groups significantly decreased their MDS-UPDRS scores, but the ketogenic group decreased more in Part 1 (-4.58 ± 2.17 points, representing a 41% improvement in baseline Part 1 scores) compared to the low-fat

group (-0.99 ± 3.63 points, representing an 11% improvement) ($P < 0.001$), with the largest between-group decreases observed for urinary problems, pain and other sensations, fatigue, daytime sleepiness, and cognitive impairment. There were no between-group differences in the magnitude of decrease for Parts 2 to 4. The most common adverse effects were excessive hunger in the low-fat group and intermittent exacerbation of the PD tremor and/or rigidity in the ketogenic group.

Conclusions: It is plausible and safe for PD patients to maintain a low-fat or ketogenic diet for 8 weeks. Both diet groups significantly improved in motor and nonmotor symptoms; however, the ketogenic group showed greater improvements in nonmotor symptoms. © 2018 The Authors. Movement Disorders published by Wiley Periodicals, Inc. on behalf of International Parkinson and Movement Disorder Society.

Key Words: Parkinson's disease; low-fat diet; ketogenic diet; MDS-UPDRS

Many new therapies for Parkinson's disease (PD) have emerged in recent decades, yet levodopa remains the primary treatment for motor symptoms. However, L-dopa is associated with the development of motor fluctuations and dyskinesias,¹ and it does not

adequately control many nonmotor symptoms,² which are often under-recognized yet ultimately more disabling than motor symptoms.^{3–6} In this context, there is growing interest in the largely unexplored, patient-empowering approach of diet manipulation.⁷

Correction added on October 24, 2018, after first print and online publication: Reference 13 has been updated in the online text and PDF versions of this article to reflect the correct citation.

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*Correspondence to: Dr. Matthew C.L. Phillips, Neurology Department, Waikato Hospital, Pembroke Street, Hamilton, NZ 3204; E-mail: Matthew.Phillips@waikatodhb.health.nz

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Preliminary evidence suggests that diet manipulation may influence motor and nonmotor symptoms in PD, yet conflict exists regarding the ideal fat to carbohydrate ratio.⁸ On one hand, a low-fat, high-carbohydrate diet may ease the passage of the dopamine precursor, tyrosine, into cerebrospinal fluid and/or trigger an insulin-induced rise in brain dopamine.^{9,10} Moreover, an increase in dietary fiber might enhance fermentation of neuroactive short-chain fatty acids in the gut, which could, theoretically, affect gut motility in PD.^{11,12} On the other hand, defects in respiratory chain complex I activity have been demonstrated in the substantia nigra (SN) and frontal cortex of people with PD^{13,14}; it has been suggested that the ketones produced by a high-fat, low-carbohydrate “ketogenic” diet may be able to circumvent this defect through a complex II-dependent mechanism, thereby enhancing mitochondrial oxidative phosphorylation in the brain.¹⁵ In addition, such a diet may also enhance central and peripheral neuron energy metabolism by stimulating mitochondrial biogenesis.¹⁶ To date, only one study has examined the effects of a ketogenic diet in PD.¹⁷ The 5 patients improved their motor scores, but in addition to the small sample size, the study was limited by a short duration of 4 weeks, the consumption of only 8% protein, which likely enhanced L-dopa bioavailability, and the lack of a control group such that a placebo effect may have contributed to the improved scores.

On this background, we designed this study to examine a general neurology hospital clinic of PD patients with regard to the plausibility and safety of maintaining a low-fat or ketogenic diet for 8 weeks, whether either diet group significantly improved in motor and/or nonmotor symptoms, and whether one group showed greater improvements compared to the other.

Patients and Methods

Overview

This was a single-phase, parallel-group (1:1 randomization) study conducted at Waikato Hospital in Hamilton, New Zealand. Waikato Hospital is a tertiary hospital serving the Waikato and Bay of Plenty regions, representing a combined population of 750,000 people. The study was approved by local Ethics and Maori Consultation Research Review Committees.

Screening

The study sought volunteers through advertisements in local and national PD newsletters in late 2016, followed by presentations at Parkinson's New Zealand meetings in Hamilton, Rotorua, and Tauranga in early 2017.

Prospective patients underwent a 2-hour screening visit in April or May 2017 with the lead investigator, nutrition specialist, and PD nurse specialist. The visit entailed

(1) a presentation of the study and diet plans, (2) a demographic, medical, and social history, (3) Montreal Cognitive Assessment (MoCA), (4) data collection for body mass index (BMI) and recommended calorie intake calculations, and (5) written informed consent.

Eligible patients were aged 40 to 75 years with a diagnosis fulfilling the UK Parkinson's Disease Society Brain Bank criteria, MoCA score > 20, BMI > 18.5, and were able and willing to follow either diet plan. Exclusion criteria were inability to speak or understand English, H & Y stages 0 or 5, or a medical, psychiatric, or substance abuse condition that in the opinion of the investigators would make it difficult to complete the study.

Patients were instructed to eat their usual, nonmodified diets from the screening visit to the start of the diet intervention and to take their L-dopa at least 1 hour before or after any meal from the screening visit to the end of the intervention.

Procedure

Patients engaged in the 8-week diet intervention from June 26 to August 18, 2017. Four 1-hour clinical visits were scheduled: two baseline visits over the 2 consecutive weeks immediately preceding the diet intervention (while on usual diet), followed by visits in weeks 4 and 8 after commencing the diet intervention.

Patients were instructed to take their medications at the same time before each visit, which involved an International Parkinson and Movement Disorder Society UPDRS (MDS-UPDRS) assessment by a diet-blinded neurologist certified by the MDS.¹⁸ It was strictly forbidden for either patient or neurologist to discuss any aspect of diet during the assessments. Patients were always assessed by the same neurologist, on the same weekday, at the same time of day. Each visit also included body weight measurements and blood tests for glycosylated hemoglobin (HbA1C), triglycerides, high-density lipoprotein (HDL), low-density lipoprotein (LDL), total cholesterol, urate, and C-reactive protein (CRP).

At the first baseline clinical visit, patients received a blood glucose and ketone (beta-hydroxybutyrate) monitor (Freestyle Neo; Abbott Diabetes Care, Whitney, UK) and finger prick training.¹⁹ After the first baseline visit but before the second visit, patients were randomized (1:1 allocation) to a low-fat or ketogenic diet plan using an online randomization generator.²⁰ To avoid selection bias, all patients were randomized simultaneously, stratified by recommended calorie intake (<2,000, 2,000–2,500, and >2,500 kcal per day, block size of two). Randomization was generated by the lead investigator, witnessed by the PD nurse specialist, and signed and dated by both. Patients received their randomized plan at the second baseline visit and commenced the plan at the start of the following week, returning for repeat clinical visits in weeks 4 and 8 after commencing the plan.

Both 4-week diet plans included weekly shopping lists containing ingredients readily available at local supermarkets, daily set menus with space to tick the completion of each meal as well as record daily (bedtime) blood glucose and ketone levels, and simple recipes (for diet plan details, see the Supplementary Appendix). The low-fat plan provided 1,750 kcal per day composed of 42 g of fat (10 g saturated), 75 g of protein, 246 g net carbohydrate, and 33 g of fiber, and for those with higher energy needs, ad libitum “calorie-booster” recipes each providing on average 500 extra kcal composed of 4 g of fat (1 g saturated), 6 g of protein, 102 g net carbohydrate, and 13 g of fiber. The ketogenic plan provided 1,750 kcal per day composed of 152 g of fat (67 g saturated), 75 g of protein, 16 g net carbohydrate, and 11 g of fiber, with each calorie-booster recipe providing on average 500 extra kcal composed of 50 g of fat (22 g saturated), 6 g of protein, 5 g net carbohydrate, and 4 g of fiber.

Regular support and education sessions were provided. The lead investigator and nutrition specialist sent global e-mails to all patients every second day and filmed and posted 10-minute videos on the study’s website every weekend. Both diets were equally presented as potentially conferring health benefits, and both groups were consistently reminded to eat until satiated.

Primary and Secondary Outcomes

Primary outcomes were within- and between-group changes in MDS-UPDRS Parts 1 to 4 from the mean of the two baseline clinical visits to week 8 after commencing the diet intervention. Secondary outcomes were within- and between-group changes in metabolic parameters, including weight, BMI, HbA1C, triglycerides, HDL, LDL, total cholesterol, urate, and CRP.

Statistical Analysis

Sample-size calculations were based on previous studies showing the smallest clinically meaningful MDS-UPDRS score improvement to be −2.64 points in Part 1, −3.05 points in Part 2, and −3.25 points in Part 3^{21,22}; to our knowledge, a clinically meaningful change in Part 4 has not been determined. To obtain 80% power using a significance level of 0.05, we calculated that 32 patients (16 per diet group) would detect a Part 1 change of 2.64 ± 2.64 points and/or Part 2 change of 3.05 ± 3.05 points and/or Part 3 change of 3.25 ± 3.25 points. Given that previous studies involving ketogenic diets in adults show an average dropout rate of 40% to 50% over 3 to 12 months,²³ we aimed to recruit 40 to 60 patients.

Given the finite sample size and pre-study uncertainty as to whether data would be normally distributed or not, all outcomes were analyzed using nonparametric tests (Wilcoxon signed-rank test for within-group comparisons, Mann-Whitney U test for between-group

comparisons). Statistical tests were two-tailed and used a significance level of 5%. All data are presented as mean $\pm$ standard deviation unless stated otherwise.

We analyzed primary and secondary outcomes using data from all randomized patients, with missing data imputed using regression imputation. To evaluate the robustness of the primary outcome findings to various imputation conditions, we additionally performed sensitivity analyses on all primary outcomes using mean imputation, baseline observation carried forward, median imputation, and complete case analyses.

Results

Patient Flow and Baseline Characteristics

Details of patient flow, including all study exclusions and withdrawals, are shown in Figure 1. We randomized 47 patients, of which 44 commenced the diets and 38 completed the study (86% completion rate for patients commencing the diets); 6 patients withdrew for reasons unrelated to the diets and 3 patients withdrew as a result of diet-related difficulties. Randomized patient baseline characteristics are shown in Table 1. There were no significant between-group differences in any baseline characteristics.

Blood Glucose and Ketone Levels

Patient-monitored blood glucose and ketone levels are shown in Figure 2. Over the 8-week diet intervention, the two diet groups significantly differed in mean weekly bedtime blood glucose (low-fat group: 6.28 ± 0.73 mmol/L vs. ketogenic group: 5.70 ± 1.20 mmol/L; $P = 0.001$) and ketone (0.16 ± 0.05 mmol/L vs. 1.15 ± 0.59 mmol/L; $P < 0.001$) levels.

Changes in MDS-UPDRS Parts 1 to 4 and Metabolic Parameters

We confirmed that patients in both diet groups took their L-dopa at the same time before each visit by measuring the time interval from the last clinically relevant (taken within the previous 8 hours) L-dopa dose to MDS-UPDRS assessment, which did not significantly differ between any two clinical visits within either group (low-fat group: 128 ± 56 minutes at baseline, 126 ± 58 minutes in week 4, 131 ± 79 minutes in week 8, $P > 0.05$; ketogenic group: 93 ± 50 minutes at baseline, 92 ± 61 minutes in week 4, 88 ± 51 minutes in week 8, $P > 0.05$).

Changes in MDS-UPDRS Parts 1 to 4 are shown in Table 2. Both diet groups significantly decreased in Part 1 (low-fat group: $P = 0.030$ vs. ketogenic group: $P < 0.001$), Part 2 ($P = 0.011$ vs. $P < 0.001$), and Part 3 ($P < 0.001$ vs. $P < 0.001$); the low-fat group showed no change in Part 4 ($P = 0.13$) whereas the ketogenic group decreased in Part 4 ($P = 0.005$). The ketogenic

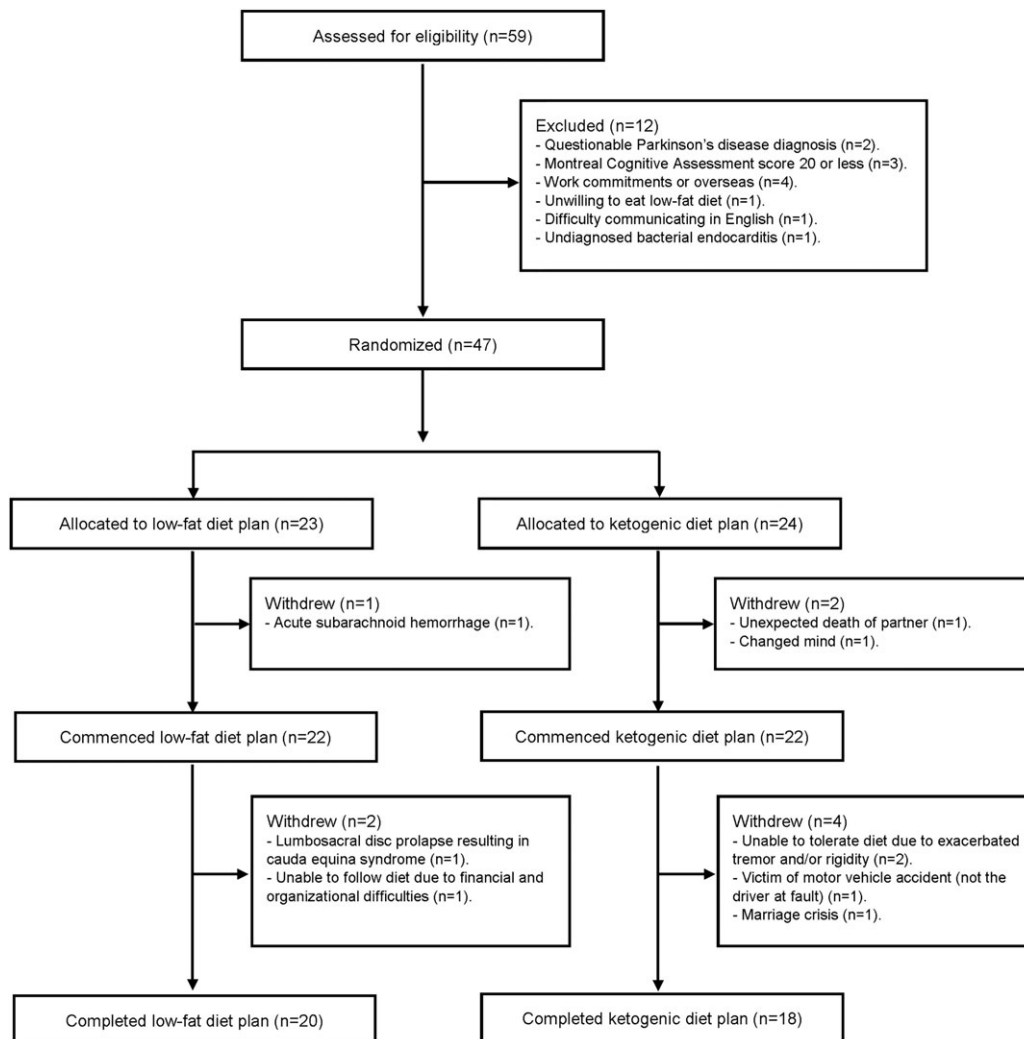


FIG. 1. Patient flow.

group showed a larger magnitude of decrease in Part 1 ($P < 0.001$), with the largest between-group decreases observed for urinary problems (-0.70 points difference), pain and other sensations (-0.64 points difference), fatigue (-0.50 points difference), daytime sleepiness (-0.45 points difference), and cognitive impairment (-0.27 points difference). There were no between-group differences in the magnitude of decrease for Part 2 ($P = 0.11$), Part 3 ($P = 0.055$), or Part 4 ($P = 0.32$). The within- and between-group comparisons of changes in Parts 1 to 4 remained similar, and the statistical conclusions unchanged, in all four sensitivity analyses (for details, see Table S1 in the Supplementary Appendix).

Changes in metabolic parameters are also shown in Table 2. Both diet groups significantly decreased in weight and BMI ($P < 0.001$ for all within-group comparisons), but there were no between-group differences in the magnitude of weight loss ($P = 0.55$) or BMI decrease ($P = 0.30$). The low-fat group did not change in HbA1C ($P = 0.92$) whereas the ketogenic group

decreased in HbA1C ($P = 0.032$), although with the exclusion of 1 outlier, a patient with type 1 diabetes whose HbA1C decreased by -19.5 mmol/mol, the magnitude of HbA1C decrease in the ketogenic group lessened considerably (from -1.42 ± 4.12 mmol/mol to -0.64 ± 1.49 mmol/mol). There were no between-group differences in the magnitude of change in HbA1C ($P = 0.095$). There were no within-group changes in triglycerides (low-fat group: $P = 0.19$ vs. ketogenic group: $P = 0.55$), nor were there any between-group differences ($P = 0.46$). The low-fat group decreased in HDL ($P = 0.027$), LDL ($P < 0.001$), total cholesterol ($P < 0.001$), and urate ($P = 0.004$) whereas the ketogenic group increased in HDL ($P < 0.001$), LDL ($P < 0.001$), total cholesterol ($P < 0.001$), and urate ($P = 0.004$), with notable between-group differences observed for all four parameters ($P < 0.001$ for all between-group comparisons). There were no within-group changes in CRP ($P = 0.47$ vs. $P = 0.12$), nor were there any between-group differences ($P = 0.10$).

TABLE 1. Randomized patient baseline characteristics.

	Low-fat group (n=23)	Ketogenic group (n=24)
Age (years)	61.48 ± 7.12	64.29 ± 6.69
Sex (male)	14 (61%)	17 (71%)
Ethnicity		
European	22 (96%)	22 (92%)
Maori	0	2 (8%)
Asian	1 (4%)	0
Functional ability		
Spouse at home	20 (87%)	21 (88%)
Screening MoCA	25.4 ± 2.0	25.3 ± 2.5
H & Y	1.78 ± 0.82 (range, 1-4)	2.13 ± 0.76 (range, 1-4)
MDS-UPDRS		
Part 1 (nonmotor daily living experiences)	8.96 ± 4.34	11.15 ± 4.15
Part 2 (motor daily living experiences)	11.13 ± 5.59	12.75 ± 5.30
Part 3 (motor examination)	34.93 ± 13.40	36.48 ± 13.29
Part 4 (motor complications)	4.33 ± 4.44	4.90 ± 3.95
PD meds		
None	4 (17%)	1 (4%)
Monoamine oxidase B inhibitor	5 (22%)	4 (17%)
Dopamine agonist	5 (22%)	10 (42%)
L-dopa	18 (78%)	22 (92%)
Catechol-O-methyl transferase inhibitor	2 (9%)	4 (17%)
Amantadine	4 (17%)	3 (13%)
Apomorphine	0	1 (4%)
Comorbidities		
Type 1 diabetes	0	1 (4%)
Type 2 diabetes	1 (4%)	0
Cholecystectomy	1 (4%)	1 (4%)
Past renal stones	1 (4%)	3 (13%)
Past gout	2 (9%)	1 (4%)
Physical profile		
Weight (kg)	78.13 ± 19.45	83.71 ± 19.38
BMI	26.96 ± 6.35	27.77 ± 5.29
Recommended calorie intake (kcal per day)	2,236 ± 430	2,242 ± 417
Blood profile		
HbA1C (mmol/mol)	34.67 (5.32%) ± 5.22	36.15 (5.46%) ± 8.60
Triglycerides (mmol/L)	1.71 ± 0.88	1.81 ± 1.18
HDL (mmol/L)	1.51 ± 0.47	1.50 ± 0.44
LDL (mmol/L)	2.74 ± 0.82	2.73 ± 1.06
Total cholesterol (mmol/L)	5.03 ± 1.00	5.03 ± 1.05
Urate (mmol/L)	0.30 ± 0.08	0.30 ± 0.08
CRP (mmol/L)	2.95 ± 2.99	1.95 ± 1.59

Except for % variables, values are presented as mean ± standard deviation.

Baseline values were obtained by averaging the two baseline clinical visits; 1 patient withdrew post-randomization, several hours before their scheduled second baseline visit, so the first visit was used as the baseline value.

Adverse Effects

Adverse effects are shown in Table 3. In the low-fat diet group, the most common adverse effect was excessive hunger, which occurred in 5 patients in weeks 1 to 4 and 6 patients in weeks 5 to 8. In the ketogenic group, the most common adverse effect was exacerbated tremor and/or rigidity, which occurred in 12 patients in weeks 1 to 4 and 7 patients in weeks 5 to 8.

Daily medication doses were altered in 6 patients. In the low-fat diet group, 1 patient self-decreased L-dopa attributed to improved motor symptoms and another with pre-existing postural hypotension and falls required increased midodrine attributed to ongoing falls. In the ketogenic group, 1 patient required

decreased L-dopa and ropinirole attributed to agitation (resolved), another required decreased pramipexole attributed to visual hallucinations (resolved), another required decreased L-dopa, ropinirole, and apomorphine attributed to exacerbated dyskinesias (partially resolved), and another with type 1 diabetes self-decreased insulin attributed to improved blood glucose control.

Discussion

We have shown, in a general neurology hospital clinic of PD patients, that it is plausible and safe to

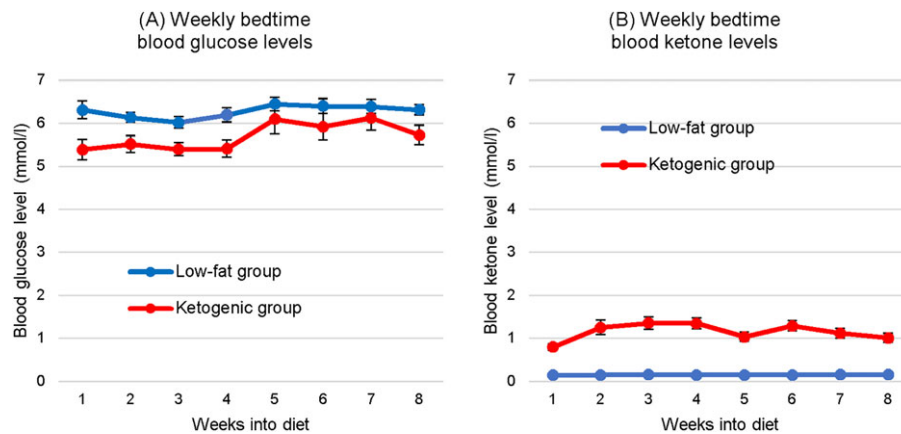


FIG. 2. Mean weekly bedtime blood (A) glucose and (B) ketone (beta-hydroxybutyrate) levels ($n=23$ for the low-fat diet group, $n=24$ for the ketogenic group). Data were missing for 16.3% of the recordings (1.8% of the 38 complete recordings, 77% of the 9 withdrawal recordings). Days missing data were left blank, with the weekly mean calculated using the remaining days of the week. Error bars indicate standard error.

maintain a low-fat or ketogenic diet for 8 weeks. Both diet groups significantly improved in motor and non-motor symptoms, but the ketogenic group showed greater improvements in nonmotor symptoms. Adverse effects were generally mild and differed between the two groups.

Several study strengths should be highlighted. First, we utilized a one-phase design, strictly enforced consistent timing, diet-blinded neurologists, and the MDS-UPDRS

(a validated rating scale with high internal consistency in measuring motor and nonmotor symptoms)¹⁸ to minimize assessment bias. Second, our diet plans utilized recipe ingredients readily available at local supermarkets, with an emphasis on affordability and palatability—thus, we chose not to use regular supplements in either plan (in particular, we chose not to supplement the ketogenic diet with medium-chain triglyceride supplements, which are not available at some supermarkets, are relatively

TABLE 2. Changes in MDS-UPDRS Parts 1 to 4 and metabolic parameters.

	Low-fat group ($n=23$)			Ketogenic group ($n=24$)			<i>P</i> Value (between groups)
	Baseline	Week 8	Change	Baseline	Week 8	Change	
Part 1 (nonmotor daily living experiences)	8.96 ± 4.34	7.96 ± 6.56	-0.99 ± 3.63	11.15 ± 4.15	6.57 ± 4.09	-4.58 ± 2.17	<0.001
Part 2 (motor daily living experiences)	11.13 ± 5.59	9.80 ± 6.81	-1.33 ± 3.28	12.75 ± 5.30	9.62 ± 5.64	-3.13 ± 4.01	0.11
Part 3 (motor examination)	34.93 ± 13.40	26.36 ± 13.58	-8.58 ± 5.50	36.48 ± 13.29	30.20 ± 12.88	-6.27 ± 4.07	0.055
Part 4 (motor complications)	4.33 ± 4.44	3.54 ± 4.86	-0.79 ± 2.71	4.90 ± 3.95	3.33 ± 3.02	-1.56 ± 2.45	0.32
Weight (kg)	78.13 ± 19.45	73.26 ± 17.99	-4.87 ± 2.47	83.71 ± 19.38	79.34 ± 17.13	-4.37 ± 3.00	0.55
BMI	26.96 ± 6.35	25.28 ± 5.95	-1.67 ± 0.79	27.77 ± 5.29	26.31 ± 4.46	-1.46 ± 1.01	0.30
HbA1C (mmol/mol)	34.67 ± 5.22	34.18 ± 3.74	-0.49 ± 2.72	36.15 ± 8.60	34.72 ± 5.68	-1.42 ± 4.12	0.095
Triglycerides (mmol/L)	1.71 ± 0.88	1.45 ± 0.55	-0.26 ± 0.74	1.81 ± 1.18	1.71 ± 0.81	-0.10 ± 0.63	0.46
HDL (mmol/L)	1.51 ± 0.47	1.40 ± 0.38	-0.11 ± 0.22	1.50 ± 0.44	1.89 ± 0.75	+0.40 ± 0.59	<0.001
LDL (mmol/L)	2.74 ± 0.82	2.35 ± 0.77	-0.40 ± 0.30	2.73 ± 1.06	3.42 ± 1.37	+0.70 ± 0.67	<0.001
Total cholesterol (mmol/L)	5.03 ± 1.00	4.40 ± 0.93	-0.63 ± 0.51	5.03 ± 1.05	5.98 ± 1.39	+0.94 ± 0.80	<0.001
Urate (mmol/L)	0.30 ± 0.08	0.28 ± 0.08	-0.02 ± 0.03	0.30 ± 0.08	0.33 ± 0.08	+0.03 ± 0.05	<0.001
CRP (mmol/L)	2.95 ± 2.99	1.95 ± 1.79	-1.00 ± 3.57	1.95 ± 1.59	2.24 ± 1.26	+0.29 ± 1.93	0.10

Values are presented as mean ± standard deviation.

Bolded values highlight changes in scores and parameters; due to round-off, some change values differ by 0.01 from the absolute value differences.

P values refer to changes in scores and parameters between (not within) groups.

TABLE 3. Adverse effects experienced at any time during the study.

	Low-fat group (n=23)		Ketogenic group (n=24)	
	Weeks 1-4	Weeks 5-8	Weeks 1-4	Weeks 5-8
Exacerbated tremor and/or rigidity	3 (13%)	5 (22%)	12 (50%)	7 (29%)
Increased irritability	4 (17%)	3 (13%)	8 (33%)	2 (8%)
Excessive hunger	5 (22%)	6 (26%)	4 (17%)	1 (4%)
Excessive thirst	1 (4%)	3 (13%)	6 (25%)	5 (21%)
Feeling lightheaded	2 (9%)	4 (17%)	2 (8%)	2 (8%)
Nausea	0	0	7 (29%)	3 (13%)
Sugar cravings	2 (9%)	1 (4%)	3 (13%)	3 (13%)
Palpitations	1 (4%)	3 (13%)	1 (4%)	2 (8%)
Headache	1 (4%)	1 (4%)	2 (8%)	2 (8%)

costly, and can produce adverse gastrointestinal effects). Third, protein intake was approximately 1 g per kg of body weight per day within each diet group and equal between groups; this is critical, given that low-protein diets containing 0.5 to 0.8 g of protein per kg of body weight per day enhance L-dopa absorption compared to high-protein diets, which may improve motor symptoms and exacerbate dyskinesias in some people with PD.²⁴⁻²⁶ Fourth, our protocol involved multimedia supports, such as weekly educational videos, designed to mitigate the patient losses traditionally associated with studies involving ketogenic diets in adults,²³ which probably contributed to the low number of patient withdrawals attributed to diet-related difficulties (3 patients).

Certain study weaknesses warrant mention. First, the study population and duration were small; a larger sample size or longer diet intervention would have increased the statistical power or provided additional time, either of which may have enabled the detection of further significant differences between the diet groups. Thus, our findings should be viewed as preliminary. Second, there were 9 patient withdrawals; imputation techniques were used to replace the missing data. To assess the robustness of our primary outcome findings, we additionally performed sensitivity analyses on all primary outcomes using mean imputation, baseline observation carried forward, median imputation, and complete case analyses.

Patient adherence to each diet plan was monitored directly and indirectly. Rather than use food diaries, which may be perceived as burdensome,²⁷ we directly monitored diet adherence by simply ensuring that patients ticked the day-to-day completion of each set meal as they proceeded. Perhaps more important, we indirectly monitored diet adherence by training patients to self-monitor their daily blood glucose and ketone levels throughout the study; we chose blood pinprick testing as it is easier, more specific, and more accurately reflects ketone levels compared to urine dipstick testing.²⁸ Using blood monitors, the low-fat diet group measured negligible ketone levels, whereas the ketogenic group demonstrated a mean weekly blood ketone level of 1.15 ± 0.59 mmol/L consistent with a state of

physiological ketosis, a coordinated metabolic response in which the liver provides ketones as an alternative, fat-derived fuel source when body glucose reserves are in short supply.²⁹

Both diet groups significantly improved their MDS-UPDRS scores over the 8-week diet intervention. It is tempting to speculate that the low-fat diet increased brain dopamine levels and/or gut short-chain fatty acid production and that the ketogenic diet enhanced central and peripheral neuron energy metabolism. However, despite being reminded to eat until satiated, the average patient in both groups lost 4 to 5 kg. It is well documented that overweight patients on unrestricted low-fat and low-carbohydrate diets can still experience significant weight loss, which may relate to altered levels of energy-regulating hormones such as insulin.^{30,31} Although weight loss is often associated with a negative impact on PD severity,³² a recent study has shown that patients with metabolic syndrome experience greater PD progression over time, mainly as a result of increased motor scores, compared to patients without metabolic syndrome.³³ Given that the average patient in both groups lost 4 to 5 kg, yet remained overweight at week 8, the observed weight loss may have contributed to the improved motor scores in both groups. In addition, the placebo effect may significantly impact motor symptoms in PD patients.^{34,35} Since our protocol included multimedia supports designed to mitigate patient withdrawals, it is also possible that a placebo effect contributed to the improved motor scores in both groups. The potential effects of both weight loss and a placebo effect must be kept in mind when interpreting the within-group comparisons.

Both diet groups improved in Part 1 (nonmotor daily living experiences), but the ketogenic group improved more; every single patient in the ketogenic group improved in Part 1, resulting in a substantial 41% reduction in baseline Part 1 scores (as opposed to 11% in the low-fat group) over the 8-week diet intervention. The robustness of this between-group finding to various imputation conditions was confirmed with multiple sensitivity analyses, including the conservative baseline observation carried forward method, which assumed

that none of the 6 patient withdrawals from the ketogenic group would have improved in Part 1 at all. This is a potentially important finding, given that nonmotor symptoms ultimately represent the most disabling aspect of PD—for example, depression alone may have over twice the impact of motor symptoms on health.⁴ Moreover, nonmotor symptoms, such as urinary problems, pain, fatigue, daytime sleepiness, and cognitive impairment, are among those least responsive to L-dopa,^{2,36} yet these are the nonmotor symptoms that improved the most in the ketogenic group compared to the low-fat group in our study. Since the magnitude of weight loss and BMI decrease were similar between groups, and the protocol and assessments were applied equally to both groups excepting the diets, neither weight loss nor a placebo effect explains the between-group differences in nonmotor symptom improvements.

Perhaps unsurprisingly, the low-fat diet group showed decreases, whereas the ketogenic group showed increases, in HDL, LDL, total cholesterol, and urate. The health benefits of lower versus higher LDL and total cholesterol in PD are debatable, with some studies correlating higher LDL and total cholesterol levels with a lower risk of PD.^{37,38} The association between urate levels and PD is less controversial, with higher serum urate levels predicting a slower rate of PD progression.³⁹

Interestingly, the adverse effect profile differed between the two diet groups. The most common adverse effect in the low-fat group was excessive hunger. In contrast, the most common adverse effect in the ketogenic group was an intermittent exacerbation of the PD tremor and/or rigidity, which resulted in 2 patient withdrawals from this group at the end of week 1. Although this adverse effect improved or resolved in many patients in weeks 5 to 8, suggesting that it was a largely transient phenomenon, it may still have impacted the Part 3 (motor examination) scores to some extent at week 8. We can only speculate as to the reason the ketogenic diet exacerbated the PD tremor and/or rigidity in some patients, but it is conceivable that the abrupt increase in fat intake temporarily augmented dopamine depletion and/or oxidative stress in the SN, followed by an adaptive response over time.⁴⁰

In conclusion, this pilot randomized, controlled trial shows that modified diets based on readily available ingredients, with normal protein levels, are plausible and safe treatment approaches in PD, with the ketogenic diet leading to greater improvements in many of the more disabling, less L-dopa-responsive nonmotor symptoms. It is possible that a ketogenic diet could play a complementary role alongside L-dopa in the treatment of PD, but due to the preliminary nature of our findings, larger and longer randomized, controlled studies are needed before this can be stated with confidence. ■

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Supporting Data

Additional Supporting Information may be found in the online version of this article at the publisher's web-site.