Preliminary Communication

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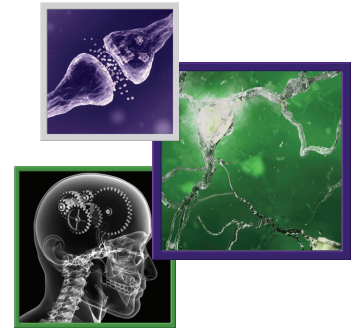
Neurodegenerative Disease Management



Effects of an low carbohydrate/healthy fat/ketogenic diet on biomarkers of health and symptoms, anxiety and depression in Parkinson's disease: a pilot study

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Aim: To evaluate a low carbohydrate/healthy fat/ketogenic diet (LCHF/KD) on symptoms, depression, anxiety and biomarkers in adults with Parkinson's disease (PD). **Patients & methods:** 16 adults ages 36–80 with PD participated in the intervention for 12 weeks. The study provided pre-post-study comparisons of biomarkers, weight, waist measurement, united Parkinson's Disease Rating Scale (UPDRS), Parkinson's Anxiety Scale (PAS) and Center for Epidemiologic Studies Depression Scale Revised-20 (CESD-R-20) Depression Scale. **Results:** Although LCHF/KD improves blood glucose in diabetes and seizure control in epilepsy, research gaps exist in this dietary intervention in PD. Statistically, significant improvements occurred in several measurements, PAS scores and Part I of the UPDRS. **Conclusion:** The LCHF/KD shows positive trends with improvements in biomarkers and anxiety symptoms. Further research is needed to evaluate dietary interventions for PD.

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Keywords: anxiety • depression • ketogenic diet • metabolic disease • nutrition • Parkinson's disease • symptoms of Parkinson's disease

People with neurodegenerative diseases (NDD), like Parkinson's disease (PD) are individuals who suffer from a progressive loss of central nervous system functions. The number of affected individuals is expected to increase to 70 million patients by 2030 and 106 million by 2050 [1]. According to the National Institutes for Health and Care Excellence (2017), recent studies have focused on a more natural approach to control motor and non-motor symptoms like tremors, rigidity, depression, anxiety and cognitive decline. These studies add to the body of knowledge of alternative therapeutic approaches to managing symptoms in Parkinson's Disease. The mounting evidence presents nonpharmacological treatments as viable treatments adding to therapeutic options [2]. In addition, research evidence suggests a low carb/high fat (LCHF)/ketogenic diet (KD) is a beneficial treatment of chronic diseases such as obesity, diabetes, cardiovascular disease and in applications for NDDs, specifically, Parkinson's disease [3].

Krikorian *et al.* demonstrated that the use of short-term, therapeutic carbohydrate restriction (<20 g daily) improved performance on memory tests in older adults with PD and mild cognitive impairment (MCI) [4]. The Krikorian study suggests a potential therapeutic role for carbohydrate restriction (LCHF) and nutritional ketosis for cognition in PD with MCI.

In a systematic review by Dewsbury *et al.*, the authors addressed the problems associated with diminished or disordered glucose metabolism in the brain, which often precedes any clinical symptoms associated with NDDs [5]. An overall analysis of the 17 study articles revealed that through the use of LCHF, which induced therapeutic ketosis (ketones <0.5 mmol), improvements were noted in cognitive measures, brain ketone utilization and general health [5]. The Dewsbury *et al.* systematic review supports the use of LCHF/KD in positive effects on brain function and general health, both foundations for our study [5].

Future Medicine

This one-group, pre-test/post-test pilot study explores the role of a low carbohydrate/healthy fat/ketogenic diet on motor symptoms, anxiety and depression, and general health biomarkers in participants with PD after 12 weeks. (International Standard Randomised Controlled Trial Number [ISRCTN] Registry # 38010).

Materials & methods

Process

Eligible participants attended a 2-h pre-study screening visit with the research team, which included the United Parkinson's Disease Rating Scale (UPDRS) Part 1–4, Parkinson's Anxiety Scale (PAS) and Center for Epidemiologic Studies Depression Scale-Revised (CESD-R-20) scales. Participants obtained pre-study bloodwork with written results received and were provided education/training on the dietary intervention and associated materials.

During the 12-week intervention, participants monitored food intake using either a written food log or My fitnesspal.com. In addition, they followed the educational materials provided for the diet and tested their blood glucose/ketones weekly using the Keto Mojo Blood meter. All participant educational materials were used with permission from Matthew Phillips from the Waikato Hospital study in Hamilton, New Zealand, in 2018. Our study's data to check for dietary compliance was gathered from reports generated by the Myfitness.pal app, similar to the study by Phillips *et al.* [3].

After 12 weeks, post-study assessment interviews were scheduled using a private, secure, online appointment site (Signup Genius), a password-protected appointment website application, and conducted in 2-h, individual, online Zoom visits. Participants obtained post-study blood work, which was compared with pre-study blood work results. H-Y staging was reported by patients' neurologists.

Depression scale

The scale used for the study to identify symptoms of depression was the CESD-R-20, commonly used to evaluate persons with PD [6]. Although published over 30 years ago, this scale is still widely used to evaluate patients with depressive symptoms. Radloff conducted a brief, 20-item self-report scale normed on the general population [6].

The scale was analyzed to have high internal consistency and modest inter-rater reliability. Participants were assessed during 1-h interviews and were from one county in Missouri and one county in Maryland for a total of (n = 2846) participant scores. Participants represented a wide variety of demographics, with adequate numbers to compare variables [6]. Results were analyzed using quantitative statistics. The CESD-R-20 scale has high internal consistency, good test-retest stability, excellent concurrent validity when comparing test scores to clinical criteria, and a high level of construct validity [6]. The fact this scale, developed in 1977, is still widely recognized and used to assess symptoms of depression lends support to our use of this scale to assess symptoms of depression in PD.

Anxiety scale

The Parkinson's anxiety scale (PAS) is an appropriate scale to assess symptoms of anxiety in our study population. The scale was explicitly designed for PD participants and correlated to other widely used scales but with greater sensitivity to change. The PAS was developed by Leentjens *et al.*, with validation based on comparisons of scores for participants on the Hamilton Anxiety Rating Scale (HARS) and Beck Anxiety Inventory (BAI). Validation of the scale was conducted using a cross-sectional, international, multi-center study involving participants (n = 362) diagnosed with Idiopathic Parkinson's Disease [7]. The PAS is a 12-item, Likert-type, self-rating (or observer-rated) scale containing three subscales: persistent anxiety, episodic anxiety and avoidance behaviors. Participants were included who were diagnosed with Hoehn and Yahr (H-Y) stages I–IV, with a mean age of 65.3, consistent with our study population [7]. Internal consistency was acceptable with Cronbach's Alpha >0.70. Correlation coefficients were high when the PAS was compared with the HARS and BAI. Participants answered these questions based on their symptoms of anxiety from the onset of their PD diagnosis.

Blood monitoring

All participants were tested for markers of health. Bloodwork was done at baseline and after the 12-week dietary intervention. These variables included:

- HgAIC;
- High-density lipoprotein (HDL);
- Low-density lipoprotein (LDL);

- Triglycerides;
- C-reactive protein (CRP).

The Dietary Intervention Adjusting for BMI, the LCHF/KD generally consists of:

- 1750 kcal per day;
- 152 g of fat (67 g saturated fat) (approx. 78% fats);
- 75 g protein (approx. 17% protein);
- 16 g net of carbohydrate (approx. 3–4% carbohydrates);
- 11 g fiber (included in carbohydrate %).

A calorie-booster snack (if needed to stabilize weight) provided an extra 500 kcals composed of:

- 50 g fat (22 g saturated fat);
- 6 g protein, 5 g net carbohydrates;
- 4 g fiber [3].

Study process

Participants were scheduled for a 2-h, individual, pre-study online Zoom assessment with the Research team to receive a presentation of the study and diet plans, a demographic, medical and social history intake, the administration of the UPDRS Scale parts 1–4 (omitting the score for rigidity #22 on Part III), assessment of body mass index (BMI), education/training on the use of the dietary intervention and a written informed consent. The UPDRS could be scored through observation and self-report using the ZOOM format however #22 on Part III (Rigidity) could not be tested due to the hand-on nature of rigidity assessment. Therefore, the scoring for #22 Rigidity on the UPDRS was omitted from statistical analysis and the total score was adjusted to reflect this change. Before the study, paperwork for obtaining pre-study bloodwork, including HgA1C, triglycerides, LDL, CRP and HDL, was sent to participants with instructions to obtain their blood work before their pre-study appointment. In addition, private communication between participants and research team members was conducted via phone, Zoom, or confidential email at participant request.

Over the 12-week intervention, email, phone and/or Zoom Live communication took place a minimum of 1x/week to answer questions, provide education on specific dietary requirements, make adjustments in food selection based on patient reports, address any side effects, provide recipes and menus and direct patients to online resources for enhanced adherence. Generally, the daily nutritional intake reflected macronutrient percentages consistent with an LCHF/KD, which included fats: 78%, proteins 17% and carbohydrates 3–4% (approximately).

After 12 weeks, post-study assessments were scheduled using, SignUp Genius and conducted in 2-h, individual, online Zoom meetings. All of the pre-study assessments were given during the post-study assessment appointment including the UPDRS (Parts I–IV omitting #22 on Part III), the CESD-R-20 Depression Scale, the Parkinson's Anxiety Scale, labs to test all the health biomarkers (triglycerides, HDL, fasting insulin, HgA1C, C-reactive protein), weight, BMI and waist circumference.

Data analysis plan

Quantitative analysis

The study analysis utilized the t-test and the Wilcoxon signed-rank test [8] (for within-group comparisons for pre-study and post-study assessments of the UPDRS scale (Parts 1–4), PAS, the CESD-R-20 and bloodwork.

Pre-study and post-study assessment results were compiled and summarized using REDCap database management software and Excel spreadsheets with access solely by research team members and translated using standard Excel formulas. Demographic data was collected for purposes of running descriptive statistics (i.e., the Fisher test). All results are presented in Tables 5 & 6 for all variables. All study data were gathered using confidential patient identifiers to maintain privacy and confidentiality throughout the study. Participants' demographic information, including age, gender and H-Y Stage, was collected at the baseline appointment.

Participant demographics

Participants were recruited from the membership rolls of the Colorado Parkinson Foundation with their permission. Study participants obtained written permission from their primary care physicians verifying fitness to participate

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Table 1. Participant demographics: age, gender, H-Y stage (n = 16).

	Men		Women	
	Age <60 years	Age >60 years	Age <60 years	Age >60 years
H-Y Stage I	0	1	0	1
H-Y Stage Ia	1	2	0	1
H-Y Stage II	1	2	2	0
H-Y Stage IIa	1	2	0	0
H-Y Stage III	1	0	0	0
H-Y Stage IIIa	0	0	0	1

in the study and their current stage of PD. Those with PD H-Y Stages I–IV were deemed eligible to participate. Participants were instructed to have taken their PD medication on their routine schedule to control for any medication effects.

The mean participant age was 64.51 (SD 11.92), with an overall mean baseline H-Y stage of 1.89. Male (n = 11) participants were greater than females (n = 5). (study participant demographics are displayed in Table 1).

Inclusion & exclusion criteria

To be eligible to participate, participants must have PD, a BMI >18.5, the ability to follow assigned LCHF/KD diet, speak/understand English, Hoehn-Yahr stage I–IV, receive permission from their primary care provider and neurologist and sign the informed consent. Individuals with diabetes received a written insulin sliding scale for use during the study. Those who did not meet the above inclusion criteria were ineligible to participate.

Study design

The pre-test/post-test, one-group study quantitative pilot study, aimed to investigate the effect of a nutritional approach on PD symptoms (UPDRS scores), major blood markers of metabolic health (BMI, HgAIC, triglycerides, HDL), and symptoms of depression and anxiety in persons with PD ages 36–85. Through the use of pre-test screening assessments of surveys, password-protected food tracking using a web-based/smartphone application, weekly testing using the Keto Mojo blood glucose/ketone tracking meter, and commonly used depression and anxiety scales, baseline and post-study results were compared after 12-weeks. This study is unique, filling a gap in the research for patients with PD addressing the treatment of PD symptoms, depression, and anxiety with a nutritional approach. The analysis involved a direct comparison of the same study participants before and after the dietary intervention. Quantitative data derived from scores on the UPDRS Scale (Parts 1–4), and performance on depression and anxiety scales, reports generated from the dietary tracking application for dietary compliance recorded daily, weekly blood glucose and blood ketone testing (to test for dietary compliance), and the comparison of pre-test/post-test bloodwork results, baseline and post-study BMI and waist measurements.

Study intervention

During the 12-week intervention, participants monitored food intake using either a written food log or My fitnesspal.com, followed the educational materials provided for the diet, and tested their fasting blood glucose and ketones weekly using a Keto Mojo blood meter. The weekly blood glucose/ketone levels were used to track dietary compliance. The LCHF/KD consists of tracking macronutrients, including fats (78%), proteins (17%) and carbohydrates (3–4%) of total daily calories.

Data collection

Baseline and post-study values were collected using the REDCap Database (REDCap 10.7.1 - © 2021 Vanderbilt University, TN, USA) for all study variables. Baseline and Post-study Assessments were conducted using Zoom live meeting software. All baseline and post-study bloodwork were obtained for study biomarker variables and reported via the LabCorp password-protected confidential website. Additionally, weekly fasting glucose and ketones were tracked and analyzed for a subset of participants who maintained levels of nutritional ketosis (fasting ketones >0.5).

Data analysis

The study achieved a sample size of 16, with 0% attrition rate from initial enrollment. Data were analyzed using REDCap through the Department of Research Support at A.T. Still University, with access solely by research team

Table 2. Analysis of all study variables.

Biomarkers and variables of all participants		Difference					p-value
		N	Mean	SD	Median	IQR	
Biomarker	Test	16	-2.54	1.66	-2.24	2.21	<.0001
BMI	t						
C reactive protein	S	16	0.06	2.40	0.09	1.23	0.8999
CESD-R-20 total score	t	16	-1.25	6.69	0.50	8.50	0.4663
Fasting blood glucose reading mean	t	16	-0.65	10.47	-3.00	16.93	0.8061
Fasting insulin	S	16	-4.70	6.10	-2.45	7.30	0.0018
HDL	S	16	0.44	10.12	-0.50	8.50	0.9137
HgA1C	S	16	-0.46	0.69	-0.30	0.15	<0.0001
PAS total score	t	16	-3.06	4.06	-2.00	7.00	0.0086
Triglycerides	t	16	-13.56	30.99	-6.50	35.50	0.1004
Triglycerides to HDL ratio	t	16	-0.38	0.80	-0.10	0.73	0.0771
UPDRS Pt I subtotal 1–4 (maximum = 16)	t	16	-1.06	1.39	-1.00	2.00	0.0079
UPDRS Part II subtotal 18–31 (maximum = 108)	t	16	-3.75	13.13	-2.50	11.50	0.2711
UPDRS Part III subtotal 5–17 (maximum = 52)	S	16	-1.63	3.58	-1.50	3.00	0.0725
UPDRS Part IV total 1–31 (maximum = 176)	t	16	-6.44	15.21	-5.00	16.50	0.1112
Waist circumference	t	16	-3.84	3.21	-3.88	4.25	0.0002
Weight	t	16	16.81	11.03	-15.25	14.40	<0.0001

CSED-R-20: Center for Epidemiologic Studies Depression Scale Revised; HDL: High-density lipoproteins; IQR: Interquartile range; PAS: Parkinson's anxiety scale; SD: Standard deviation; UPDRS: United Parkinson's disease rating scale.

members and Department of Research Support at ATSU staff (REDCap 10.7.1 - © 2021 Vanderbilt University). Results were compiled using standard Excel formulas with data entry in REDCap on predesigned forms. Descriptive statistics were used for demographic data and the Wilcoxon signed-rank test to compare pre and post-treatment values for outcome measures. We utilized nonparametric statistics for those variables found to have a non-normal distribution of the data. The t-test was used for those variables demonstrating normal distribution. A comparison analysis of means and standard deviations for all variables was performed.

Results

Health biomarkers

All participants

Significant differences between baseline and post-study scores on weight (p = <0.0001), waist measurement (p = 0.0002), BMI (p < 0.000), Fasting Insulin (p = 0.00018), HgA1C (p = <0.0001), were found for all participants after 12 weeks on the study intervention (See Table 2). None of the other variables demonstrated significant differences between baseline and post-study scores (HDL, fasting glucose triglycerides, CRP).

Subsets of participants

For the subset of participants who managed to maintain a level of nutritional ketosis (n = 14), significant differences were found between baseline and post-study scores on BMI (p = <0.0001), HgA1C (p = 0.0001), fasting insulin (p = 0.0033), weight (p = <0.0001) and waist measurement (p = 0.0002). None of the other variables demonstrated significant differences between baseline and post-study scores (HDL, fasting glucose triglycerides, CRP) (Table 3).

Symptoms scales

All participants

Significant differences were found between baseline and post-study scores on the UPDRS: Part I (p = 0.00079) and the PAS (p = 0.00086). No significant differences were found for the UPDRS Part II (p = 0.2711), Part III (p = 0.0725) or Part IV (p = 0.1112). Additionally, no significant differences were found for the CESD-R-20 depression scale (p = 0.4663) compared with baseline and post-study scores.

Table 3. Analysis of subsets (n = 14).

Biomarkers		Baseline					Poststudy Phase 1					p-value
		N	Mean	SD	Median	IQR	N	Mean	SD	Median	IQR	
Biomarker	Test	14	29.34	6.85	28.42	6.98	14	26.65	5.22	25.69	5.26	
BMI	t											<.0001
C reactive protein	S	14	1.78	2.37	0.92	1.05	14	1.85	1.76	1.32	1.94	0.8077
CESD-R-20 total score	t	14	39.29	6.08	37.50	7.00	14	38.57	6.44	37.50	7.00	0.6854
Fasting glucose	t	14	101.55	16.11	100.83	13.00	14	100.75	10.36	99.75	8.33	0.7888
Fasting insulin	S	14	14.04	8.64	13.80	12.60	14	8.85	5.52	7.45	8.80	0.0033
HDL	S	14	61.29	21.32	58.00	23.00	14	62.71	27.93	58.50	23.00	1.000
HgA1C	S	14	5.78	0.42	5.80	0.20	14	5.46	0.34	5.60	0.20	0.0001
PAS total score	t	14	26.29	9.65	23.00	10.00	14	23.21	8.01	21.00	5.00	0.0079
Triglycerides	t	14	109.57	98.49	73.00	50.00	14	95.86	92.73	69.00	24.00	0.0275
Triglycerides to HDL ratio	S	14	2.46	3.73	1.15	1.42	14	2.12	3.28	1.25	0.67	0.0785
UPDRS Part I subtotal 1–4 (maximum = 16)	t	14	3.86	2.74	3.00	3.00	14	2.93	2.87	2.00	4.00	0.0129
UPDRS Part II subtotal 18–31 (maximum = 108)	t	14	30.21	17.58	25.00	6.00	14	27.36	16.44	24.50	15.00	0.4542
UPDRS Part III subtotal 5–17 (maximum = 52)	t	14	14.29	6.50	12.00	5.00	14	12.71	5.94	11.50	5.00	0.1494
UPDRS Part IV total 1–31 (maximum = 176)	t	14	48.36	25.10	41.50	10.00	14	43.00	23.78	41.50	20.00	0.2327
Waist circumference	t	14	41.68	8.30	41.00	10.50	14	38.11	6.12	36.75	6.75	0.0002
Weight	t	14	195.46	44.69	184.80	45.00	14	177.64	34.36	169.10	40.00	<0.0001

CSEDR: Center for Epidemiologic Studies Depression Scale Revised; HDL: High-density lipoproteins; IQR: Interquartile range; PAS: Parkinson's anxiety scale; SD: Standard deviation; UPDRS: United Parkinson's disease rating scale.

Subset of participants

The data analysis indicated significant differences between those participants who maintained nutritional ketosis (blood ketones >0.5 mmol), and those who did not (blood ketones <0.5 mmol) on the UPDRS: Part I (p = 0.0129) and the PAS (p = 0.0079). No significant differences were found on the UPDRS Part II (p = 0.4542), Part III (p = 0.1494), or Part IV (p = 0.2327), or on the CESD-R-20 Depression Scale (p = 0.6854) (Table 3).

Discussion

The study's main findings included significant improvements in five out of eight tested biomarkers of health after the 12-week study period for all participants. In addition, all participants demonstrated significant improvement in PAS scores after participating in the study intervention for 12-weeks. The results of this pilot study demonstrated improvements in PD symptoms, anxiety, biomarkers of health using an LCHF/Ketogenic diet for persons with PD after 12 weeks. Participants reported improvements in both motor and non-motor symptoms of PD with very mild side effects from the nutritional approach reported by the 16 participants.

Most notable of the adverse effects were gastrointestinal, headaches, mood swings or irritability, and lower energy; however, many of these subsided with the continuation of the diet guidelines [9]. The most reported adverse effect of the LCHF/KD is the onset of the 'Keto Flu', which includes diarrhea and cramps [10]. The start of the Keto Flu has been seen in the first week of the diet and is related to higher states of ketosis [11], also consistent with our participant reports. The opposite effect of the Keto-Flu, constipation, can cause severe pain and discomfort with stomach pain and cramping affecting 30–50% of participants [12]. These side effects were present in less than 1% of our participants. Other comments not associated with side effects made by our participants included the costs of obtaining whole foods, issues with spousal/family support, dietary compliance with holiday meals and social events, and concerns with the omission of favorite foods like fruit.

Finally, it is normal to have a reduction in energy in the beginning stages of a diet, as most of the highly concentrated carbohydrates and sugary foods are removed. The detox period can also cause initial mental fatigue, headaches and 'brain fog' [13]. It should be noted that there have been no serious adverse side effects reported for the KD [14]. Most of the reported side effects among our participants were consistent with those discussed above.

The few reported side effects included chronic constipation, thirst, and occasional leg cramps at night. These were short-term and easily mitigated in our study with dietary changes in food selection, the addition of electrolytes and increased water intake.

Strengths of the study included close weekly monitoring of dietary compliance with weekly coaching sessions and blood ketone self-testing to monitor levels of nutritional ketosis (>0.5 mmol). The mean ketone level for participants (n = 15) over the 12-week intervention was 0.64 mmol. One participant failed to test ketones as prescribed with some missing values, so this data was excluded from this calculation. We chose pin-prick self-testing with a Keto Mojo Blood Glucose/Ketone meter to measure dietary compliance and blood ketones, a more reliable test than measurement with urine ketone sticks [15]. Studies have shown that the presence of cerebral ketones has a neuroprotective function by reducing inflammation, which is essential for cognitive function over time [48].

Nervous system dysfunction in PD is attributed to deficits in mitochondrial activity and a lack of brain energy. These changes may also implicate the use of ketones generated by an LCHF/KD to be considered a viable treatment option [16]. Additionally, the LCHF/KD has been shown to improve symptoms in other NDDs like multiple sclerosis by limiting neurodegeneration, increasing adenosine triphosphate production and mitochondrial function and reducing oxidative stress [17]. Perhaps these biochemical changes can explain some of the improvements noted in our pilot study with non-motor symptoms of PD, including reported improvements in memory and sleep quality.

Parkinson's disease symptoms were measured at baseline and 12 weeks using the UPDRS, a valid and reliable tool. The UPDRS is widely used, generally applicable to PD, and comprises an assessment of motor and non-motor symptoms [18]. Symptoms of PD and H-Y Stage scores were verified by participant neurologists after self-report by participants if there appeared to be a discrepancy between reported values and observation by study researchers.

Next, the dietary intervention utilized patient materials from another study on an LCHF/KD in PD with permission from Matthew Phillips in New Zealand. These materials contained food lists, extensive recipes, and educational materials on the specific accepted foods and other foods to limit during the dietary intervention period. All food items are commonly available at local grocery stores in the USA.

Many dietary studies that investigate NDD symptoms using scales fail to also assess health biomarkers for a more comprehensive picture of outcomes [19]. In addition to PD symptoms scales, our pilot study examined trends in changes in biomarkers after the 12-week dietary intervention when compared with baseline results for HgA1C, triglycerides, fasting insulin, HDL, C-reactive protein, with calculations of cardiac risk ratios to determine the risk for a cardiovascular event (triglycerides/HDL).

Using common blood biomarkers, clinicians assess the need to make dietary or lifestyle changes, repeating laboratory testing to verify compliance or changes in biomarker levels, indicating a possible reduction (or elevation) of relative risk. The challenge in nutritional research is the assessment of adherence to a specific dietary approach. Researchers more accurately assess compliance by evaluating nutritional biomarkers [20]. Pico *et al.* provide a foundation for testing biomarkers (HgA1c, triglycerides, C-reactive protein, fasting insulin, HDL) in our study. Results of our pilot study biomarker testing revealed statistically significant changes in health biomarkers over 12 weeks with reductions in BMI, HgA1C, triglycerides, C-Reactive protein (an indicator of inflammation) and fasting insulin (n = 16) (Table 2). The testing of nutritional biomarkers eliminates the often subjective and inaccurate assessment of dietary compliance using food diaries.

Statistically significant increases in HDL were noted after the 12 weeks, similar to other studies on the effects of LCHF/KD on health biomarkers [21] (see Table 2). Weight loss also revealed substantial changes after the 12 weeks, with an average overall weight loss of 16.2 lbs (n = 16). According to Leehey *et al.*, excessive weight loss can sometimes be associated with negative PD symptoms. However, recent studies have demonstrated weight loss improves metabolic health with the potential to slow the progression of PD over time with improvements in motor scores when compared with patients with poor metabolic health [21].

The dietary intervention in our study recommended protein follow 0.8 g of protein per kg of body weight or 17% of total daily calories from protein sources. Carbohydrate intake was limited to 3–4% of total daily calories. Participants were instructed to take their PD medications as usual, controlling for timing on medication intake according to protein intake, concerning which they all demonstrated knowledge.

As stated above, our pilot study involved a minimum of weekly contact with all study participants for education and coaching sessions via Zoom, along with dietary adjustments for tolerance or side effects if present, offering weekly support to decrease attrition and improve compliance.

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Our pilot study also investigated any effects of the LCHF/KD on symptoms of depression, as measured by the widely used CESD-R-20 scale, and anxiety, as measured by the PAS Scale. These scales were self-survey tools where participants reported their baseline symptoms and then again after 12 weeks of the dietary intervention. Results indicated statistically significant changes in 12-week scores for the PAS, indicating that symptoms of anxiety decreased over the 12 weeks. We recognize the possible associations between weight loss and improved energy levels and self-image, potentially reducing anxiety and/or depression symptoms in some participants.

The literature reviewed identified symptoms of anxiety up to 50% more often in patients with PD than the general public for the same age range [22]. The results of our pilot study demonstrated positive trends and potential effects of the LCHF/KD on the reduction of symptoms of anxiety. There were no significant changes in self-reported depression symptoms scores after the 12 weeks. Study researchers recognize the possible effects of the placebo effect for dietary interventions and self-reported symptoms on symptom scales such as the CESD-R-20 and PAS, as well as self-reported motor and non-motor PD symptoms.

Non-motor symptoms are often the least affected by PD medications such as L-dopa [23]; however, these symptoms were reported to have improved significantly in our study. These symptoms included reducing pain, fatigue, daytime sleepiness and improving functional memory compared with baseline scores on the UPDRS and PAS scales. The generation of blood ketones has been shown to influence overall nutritional intake among patients with NDD [5]. Research provides encouraging evidence for using blood ketones to target brain biochemical and cerebral energy anomalies, which affect non-motor and cognitive symptoms of NDD [24].

Study limitations

Researchers recognize the study's small size (n = 16) and some of the difficulties with nutritional studies with the accuracy and reliability of food logs In addition, the lack of a control group may impede the discussion of the effects of the intervention and the generalizability of study results to a broader population. Our participants were recruited from a local Parkinson's support group. It is possible our study results were due to reported improved outcomes shown in other studies to be associated with persons with NDDs who participate in support groups. Other studies have shown that persons with NDDs who participate in support groups have a greater knowledge of their disease condition and are better at performing interventions due to resilience and improved self-care and support.

The study authors also recognize the limitations of using patient self-reporting surveys, food lobs, symptoms scales, or interviews. These limitations may affect the validity of the study results and may not be consistent with the results of other nutritional studies on NDDs. Our participants may have been more educated on interventions to improve function and were more motivated to participate in the nutritional approach to improve their symptoms than the general population of persons with PD. The generalizability of these results to the general PD population must be undertaken with caution.

Conclusion

Parkinson's disease is the number two NDD diagnosis, second only to Alzheimer's disease. It presents with motor and nonmotor symptoms and affects both the patient and their families. Many persons with PD have other chronic disease comorbidities, including T2D and pre-diabetes, cardiovascular disease and obesity or overweight. This study aimed to evaluate LCHF/KD on biomarkers of chronic disease, the symptoms of PD, depression, and anxiety by comparing results of blood and body weight biomarkers and scores on commonly used symptom scales pre and post-intervention. The study consisted of 16 PD (H-Y I–IV) participants required to adhere to the LCHF/KD regimen for 12 weeks. The study utilized patient materials from a previous study by Phillips *et al.* in New Zealand [3].

The results were collected and analyzed for all participants (n = 16) and separated out for those participants who completed all required steps and demonstrated compliance with dietary requirements based on weekly blood glucose and ketone readings (n = 14). The 12-week intervention yielded significant improvements in five of the eight biomarkers (BMI, weight, waist measurement, triglycerides, HgA1C, fasting insulin, HDL, CRP). All participants significantly improved their scores on the PAS anxiety scale. No improvements were noted on the CESD-R-20 scale for symptoms of depression in the 12 weeks. Despite the small number of participants, the results showed positive trends for reducing overall PD symptoms, improving biomarkers of chronic disease, and reducing anxiety in persons with PD.

Future perspective

Research gaps exist in the area of nutrition and treatment of neurodegenerative diseases (NDDs) like PD. This study emphasizes the utility of using the LCHF/KD for those with symptoms of PD, depression and anxiety. Providers should encourage exploring alternative nutritional approaches for control of these symptoms in their patients with NDDs such as PD. An evolving body of research evidence suggests positive trends in addressing psychosocial symptoms such as depression and anxiety and neurological symptoms such as PD, Alzheimer's disease and epilepsy. An existing body of research evidence has established the efficacy of this nutritional approach to the treatment of diabetes and the reduction of cardiovascular disease, obesity, polycystic ovarian syndrome, metabolic syndrome and some autoimmune diseases. Practitioners should strive not only to address PD symptoms but also to evaluate the possible reduction of other metabolic health symptoms and conditions to contribute to the overall health of their patients with NDDs.

Our study demonstrated significant differences between baseline and post-study results (12 weeks) in five out of eight biomarkers of health and two out of three symptoms scales. Therefore, research should investigate the efficacy of using the LCHF/KD in patients with PD and symptoms of depression and anxiety over an extended study period (>12 weeks) to note any additional effects of the nutritional intervention on NDDs symptoms, and stage progression in PD.

Summary points

- Persons with Parkinson's disease (PD) experience symptoms that interfere with daily life functions in mobility, balance, cognition and self-care.
- Persons with PD often experience accompanying health challenges, including comorbidities such as pre-diabetes, diabetes and cardiac events.
- Persons with PD often experience psychosocial symptoms such as anxiety and depression.
- Persons with PD can benefit from dietary interventions designed to address their health challenges and diagnosis-specific symptoms.
- A 12-week low carbohydrate/healthy fat/ketogenic diet (LCHF/KD) intervention in adults with PD can positively influence mobility, balance, cognition, self-care, anxiety and general health.
- Using a non-medication-centered approach to control symptoms in persons with PD is increasing in popularity in the PD population.
- As healthcare costs increase, it will become more crucial for persons with neurodegenerative disease conditions to self-manage their conditions due to reduced reimbursement by health insurance.
- The LCHF/KD also appears to influence the progression of PD through the reduction of symptoms.

Author contributions

The primary researcher M Tidman performed pre-study, and post-study data collection acted as the primary editing author for the study manuscript and interfaced directly with the study sponsors. The secondary author D White performed pre-study and post-study data collection and assisted in creating and editing this manuscript. The third author T White also assisted with baseline and post-study data collection and assisted in creating and editing this manuscript.

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Ethical conduct of research

The authors state that they have obtained appropriate institutional review board approval or have followed the principles outlined in the Declaration of Helsinki for all human or animal experimental investigations. In addition, for investigations involving human subjects, informed consent has been obtained from the participants involved. This study was registered with the ISRCTN Registry by the BMC Reference Number: 38010.

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