Neurodegenerative Disease Management

ISSN: (Print) (Online) Journal homepage: www.tandfonline.com/journals/inmt20

Impact of a keto diet on symptoms of Parkinson's disease, biomarkers, depression, anxiety and quality of life: a longitudinal study

Melanie M Tidman, Dawn Reid White & Tim A White

To cite this article: Melanie M Tidman, Dawn Reid White & Tim A White (13 Jun 2024): Impact of a keto diet on symptoms of Parkinson's disease, biomarkers, depression, anxiety and quality of life: a longitudinal study, Neurodegenerative Disease Management, DOI: 10.1080/17582024.2024.2352394

To link to this article: https://doi.org/10.1080/17582024.2024.2352394

NEURODEGENERATIVE DISEASE MANAGEMENT
https://doi.org/10.1080/17582024.2024.2352394

Taylor & Francis
Taylor & Francis Group

RESEARCH ARTICLE

Impact of a keto diet on symptoms of Parkinson's disease, biomarkers, depression, anxiety and quality of life: a longitudinal study

Melanie M Tidman[*,a,f,g], Dawn Reid White[a,b,c] and Tim A White[b,d,e]

[a]College of Graduate Health Studies, A.T. Still University, 800 W. Jefferson Street, Kirksville, MO 63501, USA; [b]Benard College, University of the Pacific, 3601 Pacific Ave, Stockton, CA 95211, USA; [c]Research Fellow, Evidence Synthesis Group, EBHC South America: A JBI Affiliated Group, Calle Cartavio 406 Lima, Lima, 15023, Peru; [d]School of Health Sciences, Department of Healthcare Administration, American Public University Systems, Full-time faculty, 111 West Congress Street, Charles Town, WV 25414, USA; [e]Department of Global Health Services & Administration, School of Business, University of Maryland Global Campus, 3501 University Blvd E, Adelphi, MD 20783, USA; [f]Doctor of Health Science Program, School of Health Sciences, Liberty University, 1971 University Blvd Lynchburg, VA 24515, USA; [g]PhD in Occupational Therapy Program, Dr. Pallavi Patel College of Health Care Sciences, Nova Southeastern University, 3300 S. University Drive, Fort Lauderdale, FL 33328-2004, USA

ABSTRACT

Aim: Evidence suggests low-carbohydrate diets (LCHF) may assist in treating neurodegenerative diseases such as Parkinson's disease (PD); however, gaps exist in the literature. **Patients & methods:** We conducted a small 24-week pilot study to investigate the effects of an LCHF diet on motor and nonmotor symptoms, health biomarkers, anxiety, and depression in seven people with PD. We also captured patient experiences during the process (quality of life [QoL]). **Results:** Participants reported improved biomarkers, enhanced cognition, mood, motor and nonmotor symptoms, and reduced pain and anxiety. Participants felt improvements enhanced their QoL. **Conclusion:** We conclude that an LCHF intervention is safe, feasible, and potentially effective in mitigating the symptoms of this disorder. However, more extensive randomized controlled studies are needed to create generalizable recommendations.

ARTICLE HISTORY
Received 22 December 2023
Accepted 29 April 2024

KEYWORDS
biomarkers of health; CESD-R-20; ketogenic diet; low-carbohydrate diet; Parkinson's disease; PAS; quality-of-life

1. Background

Parkinson's disease (PD) is the number two neurodegenerative diagnosis globally, second only to Alzheimer's disease (AD) [1,2]. The disease is a slow-moving progressive disorder that escalates into impairments in motor and nonmotor functions, including tremors, rigidity, gait disturbances, anxiety, depression, cognitive deficits, and interference with activities of daily living [1]. As a result of these symptoms, patients experience neuronal loss in the substantia nigra *pars compacta* with loss of striatal dopamine uptake [2]. Neurologists or movement disorder specialists are responsible for classifying PD patients in stages I-V using the Hoehn and Yahr scale to rate their impairments [3]. Although genetic mutations may be associated with PD incidence, possible nutritional and environmental causes have not been fully explored [4,5].

Current treatment for PD includes the application of Levodopa, a dopamine-like medication to alleviate symptoms [6]. Patients and medical providers are progressively interested in non-pharmacological, adjunct treatments for PD symptoms due to significant side effects in some individuals [7]. These adjunct approaches include a recent focus on individualized nutritional approaches to managing motor and nonmotor symptoms of PD and the associated symptoms of anxiety and depression [1,8–12]. The application of nutritional strategies is at the forefront of potential alternative therapies. One of the dietary tactics under investigation with increasing interest is using the low carbohydrate, ketogenic diet (KD) to treat neurodegenerative diseases. The intent is to find a more holistic approach to controlling motor and nonmotor symptoms [13]. Ketogenic diets induce nutritional ketosis (NK), leading to the production of blood ketones, particularly β-hydroxybutyrate (βHB), which may act to mitigate neurological symptoms, such as seizures in childhood epilepsy [14–16]. Study results on the effects of ketones in epilepsy with the hypothesized neuroprotective and anti-inflammatory effects of β-hydroxybutyrate are increasingly being applied in the potential mitigation

CONTACT Melanie M Tidman Tel.: +1 (505) 259 3118; mtidman@atsu.edu

Supplemental data for this article can be accessed at https://doi.org/10.1080/17582024.2024.2352394

of motor and nonmotor symptoms in PD and other neurodegenerative diseases [4,17].

The traditional Mediterranean Diet, known to be higher in healthy fats such as olive oil, was associated with neuroprotective effects in PD patients, including improved motor and nonmotor symptoms [18–23]. The KD, comprised of high fats, moderate proteins, and very low carbohydrates (ratio of 4:1 fats: proteins + carbohydrates) [4], has also been associated with improved symptoms of depression, increases in cognitive performance, and better health biomarker outcomes in PD [19–21]. Liu et al. [24] studied nutritional patterns and related PD risk and found consuming a high-quality diet could reduce the risk of increasing PD symptoms. Mischley et al. [25] studied the dietary patterns of men and women in the USA with PD and found a significant relationship between the reduction or slowing of some symptoms of PD with the intake of coconut oil, fresh vegetables, nuts, fish, spices, fresh fruit and wine [25]. Kirkorian et al. [26] studied the use of the KD for eighteen participants with PD and found significant improvements in cognitive performance compared with the high-carbohydrate group. The culmination of these results suggests neurodegenerative diseases can be characterized by metabolically impaired neuronal synapses that need alternative energy sources for more efficient function [27,28]. As a result, the presence of blood ketones in the form of βHB may assist in mitigating some of the cognitive deficits characterized as mild cognitive impairment seen in some persons with PD [8,29]. Additionally, this research suggests there may be a role for the application of KD and NK in mitigating symptoms associated with PD, depending on the stage of the disease progression [30].

Phillips et al. contrasted the use of a low-fat versus KD for persons with PD. They found that their KD group and low-fat group both experienced improvements on the United Parkinson's Disease Rating Scale (MDS-UPDRS) Part I (mentation, behavior, and mood), Part II (activities of daily living), and Part III (motor examination) scores [3]. However, the KD groups experienced much greater improvements in their Part 1 scores, and only the KD group experienced a significant improvement in Part IV (complications of therapy) scores, reflecting improvements in dyskinesias, fluctuations, and other complications [3,10].

Many studies have investigated the effects of NK produced through the consumption of a KD on symptoms associated with AD and PD [9–11,29,31]. Unfortunately, many dietary studies are observational, frequently fraught with confounding variables, inconsistently report food intake, and show poor compliance [22]. Bohnen et al. discuss further the potential reductions in cognitive decline in PD based on two schools of thought. One is the signaling hypothesis, which indicates possible epigenetic effects of βHB produced by consuming a KD on anti-inflammatory processes slowing neurodegeneration. The other is the theory of insulin resistance and the impact of this resistance on glucose metabolism in neuronal modulation of neurotransmitters affecting neuroplasticity [32].

Along with physical problems, PD patients are faced with mood disorders like depression and anxiety. Depressive disorders in the PD population occur with an average prevalence of 17% of cases [33]. Symptoms of depression are among the most common complications associated with PD and can be related to deficits in dopamine production [26,33,34]. Depression often leads to social isolation in this population, significantly interfering with their quality of life (QoL) and associated diminished motivation to access community resources [35]. In addition, depression and symptoms of anxiety intensify the fear of the potential stigma associated with demonstrable symptoms (e.g., tremors, gait abnormalities, and speech difficulties) [36]. The mixture of anxiety and depression in PD patients reduces their QoL and increases their chance of morbidity [37].

The Parkinson's Foundation indicates that anxiety is the most prevalent psychosocial condition associated with individuals suffering from PD, affecting between 25% to 43% of patients [36]. Soon after the onset of PD, patients start displaying symptoms in line with anxiety disorder as defined in the Diagnostic and Statistical Manual IV [38]. Tidman et al. discussed a trend toward improved symptoms of depression and anxiety in a small group of 16 PD patients who followed a KD for 12 weeks. While scores on a commonly used depression scale decreased, the results were not statistically significant, possibly due to the small sample size. However, there was a statistically significant decrease in scores on an anxiety scale [11]. Given the significant disruption it causes in daily life, exploring more natural approaches to managing PD-associated depression and anxiety is warranted.

The purpose of this 24-week pilot study was to investigate the effects of a KD nutritional approach for the treatment of symptoms of PD (UPDRS I and II scores), biomarkers of metabolic health body mass index (BMI), HbA1C, fasting insulin, triglycerides, hs-CRP, HDL, and total cholesterol. In addition, the study looked at symptoms of depression and anxiety in people with PD between the ages of 36–85. Furthermore, participants shared their personal experiences before, during, and after the implementation of the KD intervention in connection with their QoL.

2. Materials & methods

2.1. Study design

The study used a longitudinal pilot study design to evaluate the use of the KD for patients with PD. We employed a mixed methods strategy using qualitative and quantitative data collection and analysis. By integrating the two methods, the researchers were able to provide a detailed description of the phenomenon through triangulation, which means that the phenomenon was investigated through several lenses [29]. Using a pilot approach supports the complex phenomenon of nutrition in PD as a natural approach to reducing motor and nonmotor symptoms associated with the disease.

The qualitative portion of the study used a phenomenological approach. We anticipated using a qualitative method would provide an element not achievable by the quantitative lab work and surveys. This approach helps researchers understand the knowledge achieved through the participant's life experiences [10]. Participants focused their answers on the following key elements: what was the experience like [31], and what did we learn along the way in [27] an attempt to identify their subjective QoL. The method allowed each PD patient to describe their lived experiences and perspectives through conversational interviews [28].

2.2. Participants

An email was sent to each participant in the Phase I study [10] about the 12-week study conversion into a longitudinal (24-week) study. All participants from the Phase I study were given an equal opportunity to move forward. As a result, a convenience sampling of seven participants consented to continue. For consistency, each participant resumed their previously used participant ID number. Participants included males (5) and females (2) diagnosed with PD H-Y Stages I-IV, between the ages of 36–85, who lived in the USA and could speak and understand English. Participants who met the inclusion criteria were asked to sign an informed consent.

2.3. Inclusion & exclusion

Eligible participants had a diagnosis of PD with Hoehn and Yahr (H-Y) Stages I-IV (Table 1), a BMI >18.5, the ability to understand and follow a KD, could speak and understand English, obtained permission to participate from their primary care provider (PCP) or neurologist, completed the 12-week nutritional study, and signed the informed consent to continue in the 24-week study. Individuals with PD who were on medications for diabetes received a written insulin sliding scale from their PCP for use during the study. Individuals not meeting the above inclusion criteria were excluded from study participation.

2.4. Study intervention (classical ketogenic diet 4:1 ratio)

Participants were provided educational materials and food plans with permission from Dr. Matthew Phillips at Waikato Hospital, Waikato, New Zealand. Phillips et al. studied dietary interventions in PD, including macronutrients set for a KD of approximately 70–75% fats, 15–20% proteins, and 5–10% carbohydrates [10]. The low-fat diet intervention was based on the USDA food pyramid. The Phillips et al. study followed a traditional KD (fats: proteins/carbs = 3:1) and tested the effects of an 8-week low-fat versus KD nutritional intervention on symptoms of PD, depression, and anxiety. At the end of 24 weeks, participants were re-evaluated, allowing for a direct comparison of baseline readings on their UPDRS (parts I and II), CESD-R-20-20, and Parkinson's anxiety scale (PAS) scales (Table 2) to data received at baseline [11]. Participants were required to obtain blood work, body weight, and waist measurements, which were used to compare to their baseline lab work results [11]. Parkinson's disease medication schedules were self-adjusted around protein intake, a common practice for patients with PD [39]. The studies of Phillips et al. and Tidman et al. provided a foundation for our study design and interventions.

The 24-week KD dietary intervention adjusting for BMI consisted of the following:

- 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 carbohydrates (approx. 3–4% carbohydrates);
- 11 g fiber (included in carbohydrate %) [10,18].

2.5. Data collection

2.5.1. Quantitative

Study researchers (MT, TW) provided education on the LCHF/ KD nutritional approach for participants and their caregivers during an initial 2-h Zoom appointment. The meeting allowed the researchers to answer questions and clarify the 24-week study requirements. Initial baseline blood work was used for comparison, and all biomarkers (Supplementary 2) were redrawn to be assessed after 24 weeks. Participants recorded their blood glucose and ketones weekly using the KetoMojo Blood Glucose/Ketone meter. In addition, participants recorded their body weight using a standard scale and were asked to measure and track waist circumference at the top of the belly button for consistency.

Table 1. Summary of participant demographics.

Variables			Participants (n = 7)	Percentage
Gender		Male	5	71%
		Female	2	28%
Age		Men <60	3	42%
		Women <60	1	14%
		Men >60	2	28%
		Women >60	1	14%
H-Y stage	Stage I	Men	0	0%
		Women	1	14%
	Stage Ia	Men	0	0%
		Women	0	0%
	Stage II	Men	2	28%
		Women	1	14%
	Stage IIa	Men	2	14%
		Women	0	0%
	Stage III	Men	1	14%
		Women	0	0%
	Stage IIIa	Men	0	0%
		Women	0	0%
	Stage IV	Men	0	0%
		Women	0	0%
Baseline BMI		<25	2	28%
		>25	5	71%
Baseline waist circumference		Women <35", Men <40"	2	28%
		Women >35", Men >40"	5	71%

BMI: Body mass index.

Table 2. Statistics for variables of interest.

Biomarkers		Difference					*p*-value
		n	Mean	SD	Median	IQR	$p < 0.05$
PD symptoms	Test						
Hoehn and Yahr stages	t	7	-0.79	0.64	-1.00	1.50	0.0171†
UPDRS subtotal 1–4 (maximum = 16) motor	t	7	-1.71	1.80	-2.00	3.00	0.0453†
UPDRS subtotal 5–17 (maximum = 52) nonmotor	t	7	-1.71	4.31	-2.00	5.00	0.3331
PAS total score	S	7	-6.29	2.87	-7.00	2.00	0.0313†
Health biomarkers	Test						
Weight	t	7	-23.43	20.69	-23.00	15.60	0.0242†
BMI	t	7	-3.34	2.97	-3.03	3.40	0.0249†
Waist circumference	t	7	-5.68	5.32	-4.75	7.00	0.0302†
CESD-R-20 total score	t	7	-4.57	4.89	-4.00	8.00	0.0484†
Fasting blood glucose readings mean	t	7	-2.60	13.25	-3.00	22.93	0.5965
Fasting insulin	t	7	-7.53	8.22	-6.50	13.30	0.0516
HDL	t	7	1.14	2.19	1.00	4.00	0.2172
C-reactive protein	S	7	-1.12	2.87	-0.31	1.20	0.3750
Triglycerides	S	7	-39.43	61.69	-15.00	67.00	0.0469†
Triglycerides to HDL ratio	S	7	-1.21	2.11	-0.31	1.64	0.0469†

†Statistically significant, p-value < 0.05.
Baseline compared with 24-week study results.
BMI: Body mass index; CESD-R-20: Center for Epidemiologic Studies Depression Scale Revised; PAS: Parkinson' Anxiety Scale; PD: Parkinson's disease; S: Shapiro-Wilk; t: T-test; UPDRS: United Parkinson's Disease Rating Scale.

Participants were required to complete weekly dietary monitoring. Those with smartphone technology tracked their progress using the MyFitnessPal app. Those without access to smartphone technology were instructed to email/mail handwritten daily food logs. In addition, they were asked to track their blood glucose and ketones once per week. Food and blood glucose/ketone logs were necessary to assess dietary compliance. A co-researcher (MMT) with advanced nutrition certification for chronic diseases checked all food logs and glucose/ketone readings weekly for dietary compliance.

All study-related data were compiled and tracked using the REDCap database (REDCap 10.7.1@2021 Vanderbilt University). Participants completed the assessment according to assessment instructions. Baseline and 24-week fasting blood work results for all seven participants were obtained from LabCorp and reported to study researchers via a password-protected portal. A comparison of baseline and 24-week results for all variables can be seen in Table 2.

2.5.2. Qualitative

Participants were required to complete a qualitative interview to understand the lived experiences of persons with PD, given that they could provide first-hand descriptions of their symptoms and subjective feelings. The discussions focused on QoL at baseline and 24 weeks and included their overall experiences with the ketogenic intervention. According to Cai et al., QoL is two dimensional with an internal factor (feeling good with oneself) and an external factor (feeling good with others) [40]. Another study defined QoL as an inward perception of their condition or health outcome, which includes symptoms, treatment, and side effects leading to social, mental, and physical elements [41]. We defined the concept of QoL as the objective perspective of a person's physical, social, and mental well-being, how they perceive their health, and how they interact with others (i.e., family, friends, and coworkers).

The interviews were focused on patients with PD; however, with permission, many of the caregivers joined and participated in the interview portion of the study. Interviews were conducted between November 2020 and August 2021. Each interview consisted of five semi-structured questions (Table 3) and was audio-recorded using a face-to-face Zoom platform to protect participants due to COVID-19. The interviews were conducted by a research team member (DRW) with prior experience conducting conversational interviews. Using a conversation interview technique [42,43] makes each participant feel comfortable expressing their experiences. The interviews lasted between 30 and 60 min.

At the onset of each interview, the participants were asked to confirm their intent to proceed with the study. Field notes were jotted on the interview guide to assist with data analysis. The last question allowed each participant to add final comments or address items not asked during the semi-structured interview. The audio recordings were sent to Rev.com to be professionally transcribed verbatim and returned to the researcher within 24 h of completion. Final transcripts were uploaded into qualitative data analysis software (Atlas.ti) to assist with coding and thematic analysis.

2.6. Data analysis

2.6.1. Quantitative

Data were analyzed on the seven participants who continued on to the end of the study. The data collected involved baseline and 24-week data on all biomarkers, total scores on the CESD-R-20 and PAS, UPDRS (Parts I and II) scores, and weight, BMI and waist measurements. The UPDRS (Parts I and II) was assessed via Zoom observation by the primary researcher, an occupational therapist with 40+ years of experience working with patients with PD. All scores were determined for participants during an 'on' medication period. Both participants and their caregivers were present during the Zoom appointments. Observations by caregivers were also considered when scoring sections of the UPDRS (Parts I and II), which is now a public-domain screening tool used in PD.

Blood glucose and ketone readings were assessed for dietary compliance (glucose $<$100 mg/dl; ketones $>$0.5 mmol). All seven participants submitted glucose and ketone readings weekly for the study (Table 4). Data for all biomarkers and scale scores were analyzed using REDCap through the Department of Research Support at A.T. Still University (REDCap 10.7.1 – C_2021 Vanderbilt University). Only research team members and the Department of Research Support had access to data. Results were compiled using standard Excel formulas with data entry on predesigned forms. Descriptive statistics were used for demographic data, the Wilcoxon signed-rank test [19], and a *t*-test to compare baseline and 24-week treatment values for outcome measures. The Wilcoxon Signed Rank Test (non-parametric test) was used to analyze results for those variables where the data did not meet normality requirements (C-reactive protein, HgA1C, PAS, Triglycerides, and Triglyceride/HDL Ratio). The *t*-test was used to analyze the results of the other variables despite the small sample size, as these variable data met the requirements for normal distribution. Given the small sample size in this pilot study, the levels for identifying trends toward significance were set at a p-value < 0.05. Given the small sample size in this pilot study, the levels for identifying trends toward significance were set at a p-value of <0.05. A comparison analysis of means and standard deviations for all variables was performed, and the results are displayed in Table 2.

2.6.2. Qualitative

Interview transcripts were entered into Atlas.ti (version 11) for evaluation. The assessment followed Colaizzi's seven-step process. Colaizzi's seven steps [44] include the following: familiarization with the data, identifying significant statements of meaning, formulating meanings, clustering themes, developing a detailed description, producing the fundamental structure, and seeking verification of the fundamental structure [21]. Using a thematic analysis approach [22], the analysis was repeated following each interview to identify potential question modifications, which assisted in interpreting the interviews. The qualitative interview researcher (DRW), who has experience with qualitative conversational interviewing, compared the interviews to the audio recordings for verifications and reread them several times to gain a deep understanding of the spoken words. As an additional step, the

Table 3. Interview guide.

24-week post-LCHF/KD intervention
1. Please describe your experience with the study from its inception through the 24-week extension. Including what was easy and difficult and how you have adjusted your life to accommodate the required aspects of the study
2. Please describe your current mental QoL (how has 24 weeks of Keto changed your mental QoL?)
3. Please describe your current physical QoL (example: do you still have the same limitation; did you see any additional physical improvements?)
4. Please describe your current social QoL (especially now that COVID-19 restrictions are starting to be lifted)
5. Do you have anything else you would like to add?

LCHF/KD: Low carbohydrate high fat/ketogenic diet; QoL: Quality of life.

Table 4. 24-week Parkinson's study weekly ketone readings.

Participant ID #[†]	Weekly blood ketone reading				
	Weeks	Mean	SD	Min	Max
8	24	0.30	0.17	0.06	0.60
13	24	0.46	20.72	0.00	1.00
15	24	0.65	0.29	0.03	1.20
18	24	0.55	0.24	0.05	1.00
19	24	0.58	1.02	0.03	5.00
21	24	0.95	0.87	0.00	3.60
23	24	0.81	0.41	0.40	1.70

[†]Participants carried over their participant ID from the original pilot study [11].
SD: Standard deviation.

interviews were independently reviewed by a team member (TW), who collectively decided on codes that led to relevant quotes and quotations. Following this step, the codes were categorized into themes and subthemes to describe the lived experiences of each participant.

2.7. Qualitative trustworthiness

Qualitative research must consider trustworthiness by addressing credibility, transferability, dependability, and confirmability [20,23]. Member checking was implemented to increase credibility. Participants received a copy of their transcripts, asked for additional thoughts or corrections, and verified accuracy. In most cases, the members had no modifications; however, two participants did make corrections, which were added to the transcripts before formal coding. Two research team members analyzed data to verify appropriate coding and ensure credibility and confirmability [23]. Other trustworthiness techniques include audit trails, research team meetings, and triangulation.

2.8. Ethical consideration & data management

The current study follows all ethical considerations to follow the guidelines of the Declaration of Helsinki. The study was approved by A.T. Still University IRB (protocol #2020-058, Approval date: 16 April 2021). The study also was approved for registry by Biomedical Central with ISRCTN #38010. Written informed consent was obtained from all participants before beginning any intervention. Certain participants utilized scanning to digitize their signed informed consent forms, which were sent via email. In contrast, those lacking scanner access opted to physically mail their signed documents to the researchers. Participants were given a pseudo number at the beginning of the 12-week study [10] and followed into the 24-week extension. All documents are stored in a password-protected computer, and paper documents will be stored in a locked safe. Documents will be held for at least 5 years as federal guidelines require.

3. Results

3.1. Quantitative

3.1.1. Health biomarkers & metabolic health

Fasting blood work to assess common biomarkers for health was performed at baseline and 24 weeks. Significance levels were set at $p < 0.05$. There were significant triglyceride results ($p = 0.0469$) and near statistical significance for fasting insulin ($p = 0.0516$) at 24 weeks. Changes in hs-CRP levels ($p = 0.3750$) and HDL ($p = 0.2172$) were not statistically significant at 24 weeks. Statistically significant differences were seen in HgA1C ($p = 0.0156$) at 24 weeks. In addition to fasting blood work, other metabolic health biomarkers were evaluated. Included in these biomarkers were BMI, weight, and waist circumference. Results comparing baseline to 24-week study participant assessments demonstrated statistical significance for participant BMI changes ($p = 0.0249$), weight ($p = 0.0242$), and waist circumference ($p = 0.0302$). Variables were analyzed using *t*-test statistics due to normally distributed data despite the small sample size. Results can be viewed in Table 2.

3.1.2. Symptoms scales: PAS, & CESD-R-20 & UPDRS (Part I & II)

A comparison analysis was conducted for total scores on the PAS and CESD-R-20, commonly used symptom scales in PD. Results at 24 weeks were statistically significant for responses to CESD-R-20 depression scale questions ($p = 0.0484$). Total scores on the PAS anxiety scale were compared between baseline and 24 weeks and demonstrated statistically significant findings ($p = 0.0313$). A comparison of results for symptom scales (PAS and CESD-R-20) can be seen in Table 2.

Results of comparisons between baseline and 24-week UPDRS scores for Part I included symptoms associated with mentation, behavior, and mood indicated statistically significant results ($p = 0.0453$). Results for Part II included performance of activities of daily living, falling, freezing, sensory complaints, and tremors, which were not statistically significant ($p = 0.3331$) at 24 weeks. Results for UPDRS Part I and Part II and comparisons can be viewed in Table 2.

3.1.3. Food logs & blood ketones

Participants submitted weekly food logs via the MyFitnessPal app throughout the 24 weeks. Study researchers reviewed food logs for dietary compliance and did not include results as a part of the statistical analysis. In addition, weekly blood ketone levels were self-tested by participants using a provided blood glucose/ketone meter, and readings were submitted via secure email for review by study researchers with expertise in interpreting the presence of NK. Participants maintained an acceptable level of NK throughout the 24 weeks, further indicating compliance with dietary guidelines (0.5–2.0 mmo/l).

3.2. Qualitative

The qualitative results focused on the QoL of patients with PD from the end of the 12-week study through the completion of the study. From the interviews, 35 codes were identified. The codes were then filtered into four main themes and eleven subthemes. The four main themes are physical QoL, social QoL, mental QoL, and barriers and enablers for KD adherence. Additional quotes associated with these transcripts are listed in Supplementary 1. The following is a glimpse of how participants viewed their lived experiences from within their journey:

3.3. Theme 1: physical QoL

Participants were asked to describe their experiences from the study's inception through the 24-week extension. They explained how pleased they were to see their health biomarkers improve and the physical changes during their intervention.

> *Pretty much everything went down quite dramatically. The biggest one, I guess, was my A1C started at, I think it was 6.7, it went down to 5.6, and then, of course, my weight loss, which has been a lifelong endeavor, is a good thing. Insulin went way down; triglycerides went way down.* (015)

3.3.1. Climbing the health ladder

The health benefits each participant obtained were uniquely significant; however, they all shared dramatic improvements.

> My *Triglycerides are down from 56 to 50 and HDL went up just one. It went from 49 to 50. Hga1c is 5.6, stable from 1.56 and CRP was down from 5.96 to 0.55. Significant change from the 12-week mark. So, it means my inflammation is down.* (018)

One participant's spouse identified how much better he did when he stayed dedicated to the intervention:

> *I think he obtained market results when he would really try to stay on target with the diet and the restriction. His last blood work was significantly currently better.* (019)

3.3.2. Strength building

Physical changes increase the positive outlook on oneself and allow the individual to push forward and do more things. These feelings are noted by participant 018 when they stated:

> *Some of the issues I had was pain in the feet and pain in the knees and pain in the fingers and just overall body pain. And a lot of that has gone away. I'd say about 50% of it has gone away. Maybe more." Participant 018 went on to say, "Yeah, I'm exercising more. I was on a bicycle ride the other day and we were in the mountains and we were in the mountain bike area, and I fell down and I fell and scraped my leg. But that's okay. I don't think I would've even tried it.* (018)

The family recognized positive characteristics, which allowed them to communicate better with their loved ones.

> *I thought he could talk better. I thought his facial expression was better* (013)

3.4. Theme 2: social QoL

What is better than waking up and knowing that 'I can do anything', especially when facing a life-debilitating neurodegenerative disease process? The patients in this study described how they learned to roll with the

punches through self-realization. During this process, each participant learned how to adjust the intervention to suit their bodies and minds.

> *I feel I'm growing, and I'm just becoming more mentally prepared for the future. My goal is to master rolling with the punches, and I have an increased opportunity for those events, I think. I might as well take advantage of it and learn how to best cope with the crappy stuff in life.* (021)

3.4.1. Rolling with the punches

People confronted with a disease without a cure must rely on their resilience and learn to roll with the punches. They explained their thoughts in the following way:

> *I think I have been noticeably more relaxed about day-to-day frustrations and unexpected events that come up and have been taking them in stride for the most part.* (015)

3.4.2. Rejoining the world

Socialization includes how people learn to become an active part of society. This process includes learning how to feel accepted for who you are. Unfortunately, some people with PD feel uncomfortable in public due to their altered motor function, like tremors or soft voices.

> *The fact that I'm more confident in myself just from the way I look. Yeah. My wife says it every couple of days. It's like your shoulders are broad, and your muscles were definitely noticeably larger. So yeah, we would go out* (008)

Learning to overcome barriers and feel more confident in public is crucial to their well-being and QoL.

> *A lot of our social life is contained within the family. We get out every day to go for a ride somewhere or go get an ice cream or see to somebody.* (013)

3.4.3. Adjusting ketogenesis to my personal needs

Not everyone learning a new diet's idiosyncrasies completely understands how their body and mind will react. For some, adjusting and learning new techniques is the best way to stay compliant and meet the minimum requirements. The LCHF/Keto intervention is no different. Here are some adjustments that were made by the participants, which led to good results.

> *Regular coconut oil or avocado oil, I can down shot glasses of that and have no problem doing four of them a day, drinking it out of the bottle because it really has no flavor to it. The improvement is significant. But we had to make some changes because things just weren't quite… Now, that when we found that sweet spot life is much better, even keel, nice and smooth, smooth sailing.* (019)

Some participants we pleasantly surprised at how well they responded to the intervention.

> *I thought I was going to starve, and for a while there, I dropped probably 20 pounds. I got down to 165. Then at that point, it was like, I don't want to go any lower than that. What can I eat that doesn't break the diet but still give me the nutrition that I need?*" (018)
>
> "*We found it very easy, and only time we would have to adjust is if we went out or were at friends or family for dinner.* (013)

3.5. Theme 3: mental QoL

So often, people with neurodegenerative disorders describe how a disease negatively affects their cognition, which often leads to psychological problems like anxiety or depression. During the interviews, participants were asked about their experiences with their mental QoL over the previous 24 weeks.

> *I think I have less fogginess. I did have a lot of fogginess in my mind before the diet, and now I have less fogginess. So, it's been a very good thing for that.* (018)

3.5.1. Dusting off the cobwebs

Mental clarity addresses any aspect of cognition, including forgetfulness or feeling like you have a fog that clouds your thoughts. Participants elaborated on aspects of their cognition associated with feeling better, sleeping better, and fog lifting away. However, some participants were not as lucky.

> *I'm liking the coconut oil? I think my vocabulary and my thought process has really come around a lot." His spouse suggested "his cognition has definitely improved, especially when he's consistent on his coconut oils. When he does both the regimen of the coconut oil and the diet. The difference is huge* (019)

One individual explained how they slept better and how it helped them overall.

> *I don't feel general fatigue like I used to, and I rarely need to take a nap during the afternoon like I often would before the change in eating. I have more energy in general, partly because I have been sleeping better.* (015)

Another participant described their experience differently:

Yeah, I had no real changes to my clarity or anything like that. I was having night… Well, not night terrors. What do they call it? A REM sleep disorder, behavior or whatever, and those I thought may have slowed down during the Keto diet, but I was still having a couple a week, and just a couple of nights ago while I was asleep Rebecca said I nearly pulled her finger off and bruised it and hurt it, and her wrists, so I don't know what's going to help that, but the diet didn't really make a change. (008)

3.5.2. How is my psyche?

As described from their prior experiences, the participants struggle with bouts of anxiety, depression, and even their attitude. The following have shared their lived experiences post-intervention by stating:

The depression has been good. Anxiety is still a struggle, some, but not nearly as bad as it was the beginning of the year." (021)

"*The depression level and stuff has eased up a lot too with the diet and going to the counselor and the new meds too. I think the oil, having more fat, not have a – that deep dark depression hole to go into."* (019)

"*My attitude and my emotional outlook has improved significantly.* (023)

3.5.3. Before & after

Each participant discussed their experiences, beginning with how their life was before and what accomplishments they observed following the study. Some focused on weight loss totals, while others described pain reduction. Here are a few of their comments:

Some of the issues I had was pain in the feet and pain in the knees and pain in the fingers and just overall body pain. And a lot of that has gone away. I'd say about 50% of it has gone away. Maybe more." (018)

"*I don't really have any serious sugar cravings anymore. They probably became unnoticeable around week six or seven. So, it's been a long time since I've craved sugar."* (023)

"*I dropped probably 20 pounds". I got down to 165, and "I think I was around 185. I got down to 165, and I weighed this morning at 172.* (008)

3.6. Theme 4: barriers & enablers for KD adherence

Humans need a support system that is there when they need it the most. A family consists of a group of people, related or not, that you can rely on when life becomes stressful or difficult. In many cases, the participants describe how family support is everything to them and helps them continue.

3.6.1. I'm here for you

I will walk with you through your journey. I want you to be healthy and happy. These are the common thoughts of our participant's family members.

My son, who's 18 and way overweight, actually joined us, joined me and my fiancée, in eating the keto. I never pushed him because he's a teenager; you push them, they go the other way. But through our example, through my example, he decided it would be something good for him. And he's really come around. He's not as rigid as me, but it's pretty rigid for a teenager. And one day he was like, "Boy, this sugar really makes me feel like crap if I eat it, and then the next day I'm just sick. So, this stuff is really toxic, isn't it?" So, from his mouth, I appreciated someone of his age being able to go to that attitude as well." (023)

"*My wife is a hawk and she watches, and I'll go to get something to eat and she'll go, "Wait a minute. That's got sugar." She keeps me on track pretty well.* (008)

3.6.2. Better outlook on life

Life is about the harmony of the mind, body, and heart. Participants recognized how well their minds and bodies adjusted to the intervention, and the following changes were significantly better for their disease.

My attitude and my emotional outlook have improved significantly. (023)

3.6.3. Staying on the ketogenic path

Every participant explained how they plan to stay on the Ketogenesis diet for their health and to meet their personal goals. Here are a few of the comments.

I plan on continuing with a diet." (013)

"*I still am doing that, and my daughter is jumping back on board with me."* (021)

"*Oh, yeah. For permanent, absolutely. Definitely permanent."* (023)

"*Yeah, I'm planning on staying on it.* (008)

4. Discussion

The study aimed to understand the effects of a KD on a PD patient's biomarker levels, motor and nonmotor symptoms, depression and anxiety symptoms, and their QoL over 24 weeks. Consistent with other studies [45], our results demonstrated positive changes in the biomarkers of all seven participants, including weight loss and

decreased waist circumference as metabolic markers for improvement in insulin resistance [46]. In line with these studies, our participants witnessed a decrease in their HgA1C, triglycerides, hs-CRP, and fasting insulin while increasing their HDL (Table 2). During their interviews, they described a reduction in anxiety and depression. They also recognized numerous health benefits, including improved thinking capacity, body strength, and self-confidence, to rejoin life outside their PD bubble.

Our use of the KD was characterized by nutritional adjustments intended to produce higher levels of circulating βHB, which influences adenosine triphosphate (ATP) production in cellular structures and mitochondria in the body and the brain [9]. Dietary compliance and notations of changes in biomarkers and symptoms were evaluated by having participants provide weekly readings of blood ketone levels to verify an increased presence of ketones, indicating NK. Studies have shown that maintaining blood ketone levels produced by consuming a KD can act as enhancements for signaling molecules, thus making the ketone body βHB well-suited to potentially slow, halt, or even reverse the progression of PD [5]. Therefore, by increasing dopamine substrate expression alone, βHB produced by consuming a KD may protect against energy depletion, oxidative stress, inflammation, and apoptosis in the PD brain [5]. We can speculate, based on ours and other studies, that all improvements in cognition and mood could have resulted from the effects of NK and βHB levels in the brain [47–49], although the mechanism by which βHB might increase neurotransmitter levels in dopamine production is still under investigation. Participants sustained healthy blood glucose ($<$100 mg/dl) and ketone levels throughout the 24-week intervention using the self-monitoring devices described above ($>$0.5–2.0 mmol), consistent with other studies [50].

During qualitative post-intervention interviews, most participants stated they had a better outlook on life, felt a KD was a sustainable way of life, and shared stories of their entire family joining their new way of life. They described how they learned to build resilience through self-realization, which allowed them to recall how to believe in themselves. As such, the results of our study showed statistically significant changes in anxiety and depression levels and improvements in symptoms such as mentation, behavior, and mood, consistent with findings by Phillips et al.

Parkinson's disease patients struggle with cognitive decline, often leaving them unable to think clearly, often described as brain fog [26]. While the decline continues to progress during the disease process [51], there are instances where NK [52] has proven helpful in cases of mild cognitive impairment [26], PD, bipolar [35], sleep disruption [53], anxiety and other psychiatric disorders [9]. The participants in our study reported improvements consistent with these studies. When describing their lived experiences, they explained how eating foods high in healthy fats and oils assisted with mental clarity, which they declared helped with a better outlook. Participants also expressed their bouts of depression and anxiety were not as bad as before the intervention. In addition, our participants reported better sleeping patterns.

Another common problem with PD progression is difficulty with motor and nonmotor functionality [54]. Our study results for the UPDRS Parts I (mentation, behavior, and mood) and Part II (activities of daily living) were consistent with other studies [3]. In the Phillips et al. study, participants reported improved mobility and nonmotor symptoms after 8 weeks on a KD. Our study expanded on the findings by Phillips et al. by evaluating symptoms of depression and anxiety. In addition, participants shared stories of increased physical activities and doing things outside their past norms. One participant was excited to tell a story about attending an outdoor festival they never dreamed would happen again. Others recognized their PD symptoms decreased during the intervention, motivating them to participate in social activities they previously would have ignored.

Some participants encountered episodes of constipation side effects that were mitigated through individual discussions [54]. This problem was quickly remedied with increased water, magnesium, and salt intake [55]. Other participants promptly declared they had these same problems; however, they found using medium-chain triglycerides, coconut oil, or avocado oils as a part of the KD [29,56] helped relieve the problem. The increase in oils was also reported to reduce brain fogginess and fatigue, consistent with other studies [57].

Some patients with PD experience challenges with a KD, including financial and social concerns associated with the cost of approved foods [58]. For instance, participants on a fixed income feared that the high price of fresh meats and poultry and inadequate access to fresh vegetables would make participating difficult or out of reach. They were also concerned the intervention would interfere with holidays and social gatherings centered around non-compliant foods. Consequently, special techniques for managing these concerns were discussed, and participants were provided with an alternative list of traditional holiday foods upon request to increase compliance [13,59]. Later, participants described their experiences with social outings that were well-received and more manageable than anticipated. In the final interviews, participants expressed how willing their families were to change their eating habits when they saw the par-

ticipants' results. Several participants described how they enticed their family and friends into enjoying the foods they prepared.

4.1. Study limitations

The investigation uncovered various limitations. The primary limitation of this pilot study is the small sample size (n = 7). In addition, the seven participants were recruited after completing a 12-week study, so they may have possessed some bias as to the expected results, which may have influenced responses on the scales and measures in the study (PAS, CESD-R-20, and UPDRS: Parts I and II). It is impossible to estimate the effects of the COVID-19 pandemic on social isolation and restrictions that occurred during the study period (2020–2021). Symptoms of anxiety or depression and a lack of statistical improvement in scale scores could have occurred due to government-imposed isolation policies. Like many dietary interventions, the reliability of food records and the MyFitnessPal app may raise doubts. Participants had to record each meal after consumption to control for memory lapses and improve food tracking. Study researchers recognize the influence of self-reporting and recall bias on the food tracking written logs and app use.

An interventional study frequently presents the 'placebo' effect that may have affected participants' responses on the depression and anxiety scales and the UPDRS (Parts I and II). The pilot study's lack of a control group and the small sample size (n = 7) also affected the results' generalizability. Even though the results mostly identified positive trends ($p < 0.05$) and did not reach statistical significance, for a small study (n = 7), these trends were consistent across multiple variables. In addition, all participants reported attending a local PD support group, which may have influenced their responses. They reported improved compliance and knowledge outcomes compared with persons who did not participate in a support group.

Finally, a common issue with extended studies is high attrition rates and fatigue associated with being on the KD for 24 weeks. Our study population began with eight participants, with only one dropping out the first week due to a significant life event (attrition rate = 12.5%). The remaining seven participants thanked the researchers for explaining and helping them through the study by answering all their questions and helping them realize how easy this lifestyle could become. At the end of the study, every participant explained how they planned to stay on the KD for their health and looked forward to meeting their personal goals.

5. Conclusion

In this 24-week dietary intervention study involving seven participants with PD, the effects of a KD on various biomarkers, Parkinson's symptoms, depression, anxiety, and self-assessed quality of life (QoL) were evaluated. Baseline and 24-week measurements were conducted, including bloodwork, blood glucose, ketone levels, and scales assessing symptoms. While statistical significance ($p < 0.05$) was achieved for triglycerides, fasting insulin, HgA1C, weight, and waist circumference, other biomarkers showed positive trends without statistical significance. Participants reported weight loss, decreased waist circumference, better cognition and mood, decreased anxiety, enhanced motor symptoms, and increased engagement in social and physical activities. Qualitative interviews supported the quantitative findings, emphasizing the intervention's ease and family support. This pilot study identifies significant changes in nonmotor PD symptoms and adds to the literature on KD in PD. Future research with a more extensive, randomized control approach is needed to generalize these findings and explore dietary interventions as an alternative treatment for PD symptoms, depression, anxiety, metabolic health biomarkers, and overall QoL.

Summary points

- Parkinson's disease (PD) is the number two neurodegenerative diagnosis globally, second only to Alzheimer's disease.
- Persons with PD experience symptoms that interfere with mobility, balance, socialization, cognition, and activities of daily living.
- Persons with PD often suffer from comorbidities such as hypertension, pre-diabetes, diabetes, and cardiac events.
- Persons with PD can experience symptoms of anxiety and depression.
- Persons with PD can benefit from dietary interventions, including the ketogenic diet, to address their general health and symptoms.
- A 24-week ketogenic diet (KD) intervention in adults with PD positively influenced gait and mobility, self-care, socialization, depression and anxiety, and improved biomarkers of general health.
- A nutrition-centered approach to mitigate symptoms in persons with PD has potential applications for the PD population.
- As healthcare costs increase, it will become crucial for persons with neurodegenerative disease conditions to seek alternative strategies to manage their conditions due to issues of reimbursement and access to healthcare.

Acknowledgments

The study researchers wish to thank the Colorado Parkinson Foundation for their support and assistance with the recruitment phase of the study. Data analysis was conducted by a Statistician at ATSU's IRB statistics department using the RedCap database.

Author contributions

Conceptualization: (MM Tidman, DR White and TA White); methodology: (MM Tidman, DR White and TA White); software: (MM Tidman, DR White and TA White); validation: (MM Tidman, DR White and TA White); formal analysis: (MM Tidman, DR White and TA White); investigation: (MM Tidman, DR White and TA White); data curation: ATSU IRB; writing – original draft preparation: (MM Tidman, DR White and TA White); writing – review & editing: (TA White, DR White, MM Tidman); funding acquisition: (MM Tidman).

Financial disclosure

This research was funded by the Colorado Parkinson Foundation grant number 2021-04-16. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

Competing interests disclosure

The authors have no competing interests or relevant affiliations with any organization or entity related to the subject matter or materials discussed in the manuscript. This includes employment, consultancies, stock ownership or options, and expert testimony.

Writing disclosure

No writing assistance was utilized in the production of this manuscript.

Ethical conduct of research

The authors state that they have obtained appropriate institutional review board approval (Institutional Review Board of A. T. Still University (protocol #2020-058, Approval date: 6 April 2021) and/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.

ORCID

Melanie M Tidman https://orcid.org/0000-0002-6333-8514
Dawn Reid White https://orcid.org/0000-0001-8910-9894
Tim A White https://orcid.org/0000-0001-8550-3317

References

Papers of special note have been highlighted as • of interest; •• of considerable interest

1. Lange KW, Nakamuraa Y, Chen N, et al. Diet and medical foods in Parkinson's disease. Netherlands: Elsevier; 2019.
   •• Discusses the use of dietary interventions in neurodegeneration, including the ketogenic diet and the Mediterranean diet, and the potential effects of nutritional ketosis on symptoms in Parkinson's disease (PD). They specifically discussed the possible effects of the ketogenic diet to produce dopamine precursors for a potential positive impact on nonmotor symptom management in PD.
2. Parayath N, Pawar G, Avachat C, Miyake MM, Bleier B, Amiji MM. Chapter 8: neurodegenerative disease. Nanomedicine for Inflammatory Diseases. Boca Raton, Florida: Taylor & Francis Group; 2017. p. 289–318. doi:10.1201/9781315152356-15
3. Fahn S, Elton R. The united Parkinson's rating scale. Recent Develop Parkinson's Dis. 1987;2:153–163.
4. Yang H, Shan W, Zhu F, et al. Ketone bodies in neurological diseases: focus on neuroprotection and underlying mechanisms. Front Neurol. 2019;10:585. doi:10.3389/fneur.2019.00585
   • The effects of ketone bodies and neuroprotection in neurodegenerative diseases like PD and Alzheimer's disease (AD). They discuss the mechanisms whereby ketone bodies become an alternative fuel source for the brain, positively affecting brain energy metabolism through the reduction of oxidative stress. However, further investigation is needed to identify the specific factors in the potential mitigation of symptoms in PD and other neurodegenerative diseases.
5. Norwitz NG, Hu MT, Clarke K. The mechanisms by which the ketone body D-beta-hydroxybutyrate may improve the multiple cellular pathologies of Parkinson's disease. Front Nutr. 2019;6:63. doi:10.3389/fnut.2019.00063
6. Foundation P. Levodopa 2024. Available from: https://www.parkinson.org/living-with-parkinsons/treatment/prescription-medications/levodopa
7. Dong J, Cui Y, Li S, Le W. Current pharmaceutical treatments and alternative therapies of Parkinson's disease. Curr Neuropharmacol. 2016;14:339–355. doi:10.2174/1570159X14666151120123025
8. Kraeuter AK, Guest PC, Sarnyai Z. The therapeutic potential of ketogenic diet throughout life: focus on metabolic, neurodevelopmental and neurodegenerative disorders. Adv Exp Med Biol. 2019;1178:77–101. doi:10.1007/978-3-030-25650-0_5
   • Focused on the effects of fasting and fasting-mimicking diets, such as the ketogenic diet, on fasting glucose and insulin and the production of alternative fuel sources for the brain. They summarized that the application of approaches to increase the production of ketones may offer potential treatments for a variety of neurodegenerative diseases like PD and AD.
9. Morris G, Maes M, Berk M, Carvalho AF, Puri BK. Nutritional ketosis as an intervention to relieve astrogliosis: possible therapeutic applications in the treatment of neurodegenerative and neuroprogressive disorders. European Psychiatry. 2020;63(1):1–21. doi:10.1192/j.eurpsy.2019.13
   •• Investigated the presence of Nutritional Ketosis through diet and supplementation and its effects on oxidative stress with potential impacts on neurodegeneration. The presence of ketones in the brain produces alternative fuel with the potential to mitigate neurodegenerative changes in PD and other neurodegenerative conditions.
10. Phillips MCL, Murtagh DKJ, Gilbertson LJ, Asztely FJS, Lynch CDP. Low-fat versus ketogenic diet in Parkinson's disease: a pilot randomized controlled trial. Mov Disord. 2018;33(8):1306–1314. doi:10.1002/mds.27390

•• A comparison of nutritional approaches of low-fat versus ketogenic diets and the effects on symptoms and biomarkers in PD. This randomized controlled trial adds support for our approach and study design and contributes to the growing body of literature for alternative approaches to treatments specifically of nonmotor symptoms in PD.

11. Tidman M, White D, White T. 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. Neurodegen Dis Manage. 2022;12(2):57–66. doi:10.2217/nmt-2021-0033
12. de la Rubia Orti JE, Fernandez D, Platero F, et al. Can ketogenic diet improve Alzheimer's disease? Association with anxiety, depression, and glutamate system. Front Nutr. 2021;8:744398. doi:10.3389/fnut.2021.744398
13. Morrison S, Fazeli P, Gower B, et al. The ketogenic diet as a non-pharmacological treatment for HIV-associated neurocognitive disorder: a descriptive analysis. J Psychiat Behav Sci. 2018; 2018(3):1014. doi:10.33582/2637-8027/1014
14. Wheless JW. History of the ketogenic diet. Epilepsia. 2008;49:3–5. doi:10.1111/j.1528-1167.2008.01821.x
15. Kim DY, Simeone KA, Simeone TA, et al. Ketone bodies mediate antiseizure effects through mitochondrial permeability transition. Ann Neurol. 2015;78(1):77–87. doi:10.1002/ana.24424
16. Ozdemir R, Guzel O, Kucuk M, et al. The effect of the ketogenic diet on the vascular structure and functions in children with intractable epilepsy. Pediatr Neurol. 2016;56:30–34. doi:10.1016/j.pediatrneurol.2015.10.017
17. Egan B, D'Agostino DP. Fueling performance: ketones enter the mix. Cell Metab. 2016;24(3):373–375. doi:10.1016/j.cmet.2016.08.021
18. Rees J, Ryan J, Laws M, et al. A comprehensive examination of the evidence for whole of diet patterns in Parkinson's disease: a scoping review. Nutr Neurosci. 2023;27(6):1–19. doi:10.1080/1028415X.2023.2233727
19. Pavon S, Lazaro E, Martinez O, et al. Ketogenic diet and cognition in neurological diseases: a systematic review. Nutr Rev. 2021;79(7):802–813. doi:10.1093/nutrit/nuaa113
20. Christensen MG, Damsgaard J, Fink-Jensen A. Use of ketogenic diets in the treatment of central nervous system diseases: a systematic review. Nord J Psychiatry. 2021;75(1):1–8. doi:10.1080/08039488.2020.1795924
21. Bhuiyan AR, Payton M, Mitra AK, et al. Progression of metabolic syndrome components along with depression symptoms and high sensitivity C-reactive protein: the Bogalusa heart study. Int J Environ Res Public Health. 2021;18(9):5010. doi:10.3390/ijerph18095010
22. Weaver CM, Miller JW. Challenges in conducting clinical nutrition research. Nutr Rev. 2017;75(7):491–499. doi:10.1093/nutrit/nux026
23. Chen WW, Zhang X, Huang WJ. Role of neuroinflammation in neurodegenerative diseases (Review). Mol Med Rep. 2016;13(4):3391–3396. doi:10.3892/mmr.2016.4948
24. Liu YH, Jensen GL, Na M, et al. Diet quality and risk of Parkinson's disease: a prospective study and meta-analysis. J Parkinson's Dis. 2021;11(1):337–347. doi:10.3233/JPD-202290
25. Mischley LK, Lau RC, Bennet RD. Role of diet and nutritional supplements in Parkinson's disease progression. Oxid Med Cell Longev. 2017;2017(6405278):1143–1161. doi:10.1155/2017/6405278
26. Krikorian R, Shidler MD, Summer SS, et al. Nutritional ketosis for mild cognitive impairment in Parkinson's disease: a controlled pilot trial. Clin Parkinsonism Related Disord. 2019;1:41–47. doi:10.1016/j.prdoa.2019.07.006

•• A controlled pilot study to investigate the effects of lowering glucose and insulin resistance on mild cognitive impairment in PD through dietary carbohydrate restriction. They found cognition improved in those subjects who maintained nutritional ketosis, especially in terms of memory performance.

27. Broom GM, Shaw IC, Rucklidge JJ. The ketogenic diet as a potential treatment and prevention strategy for Alzheimer's disease. Nutrition. 2019;60:118–121. doi:10.1016/j.nut.2018.10.003
28. Davis JJ, Fournakis N, Ellison J. Ketogenic diet for the treatment and prevention of dementia: a review. J Geriatr Psychiatry Neurol. 2021;34(1):3–10. doi:10.1177/0891988720901785
29. Juby A, Blackburn TE, Mager D. Use of medium chain triglyceride (MCT) oil in subjects with Alzheimer's disease: a randomized, double-blind, placebo-controlled, crossover study,with an open-label extension. Alzheimer's Dementia. 2022;8(e12259):1–10. doi:10.1002/trc2.12259
30. Cunnane SC, Courchesne-Loyer A, St-Pierre V, et al. Can ketones compensate for deteriorating brain glucose uptake during aging? Implications for the risk and treatment of Alzheimer's disease. Ann NY Acad Sci. 2016;1367(1):12–20. doi:10.1111/nyas.12999
31. Wlodarek D. Role of ketogenic diets in neurodegenerative diseases (Alzheimer's disease and Parkinson's disease). Nutrients. 2019;11(1):169. doi:10.3390/nu11010169
32. Bohnen JLB, Albin RL, Bohnen NI. Ketogenic interventions in mild cognitive impairment, Alzheimer's disease, and Parkinson's disease: a systematic review and critical appraisal. Front Neurol. 2023;14:1123290. doi:10.3389/fneur.2023.1123290
33. Leentjens A, Dujardin K, Marsh L, Richard I, Starkstein S, Martinez-Martin P. Anxiety rating scales in Parkinson's disease: a validation study of the Hamilton anxiety rating scale, the Beck anxiety inventory, and the hospital anxiety and depression scale. Mov Disord. 2011;26::407–415. doi:10.1002/mds.23184
34. Frenklach A. Management of depression in Parkinson's disease. Am J Psychiatr Residents. 2017;11(4):8–11. doi:10.1176/appi.ajp-rj.2016.110405
35. Campbell IH, Campbell H. Ketosis and bipolar disorder: controlled analytic study of online reports. BJPsych Open. 2019;5(4):e58. doi:10.1192/bjo.2019.49
36. Foundation PS. Parkinson's Disease [Webpage]. New York, NY; 2020 [cited 2020 2.26.2020]. Available from: https://www.parkinson.org/Understanding-Parkinsons/Symptoms/Non-Movement-Symptoms/Anxiety
37. Chen JJ, Marsh L. Anxiety in Parkinson's disease: identification and management. Therap Advan Neurolog Disord. 2014;7(1):52–59. doi:10.1177/1756285613495723
38. Leentjens AFG, Dujardin K, Pontone GM, Starkstein SE, Weintraub D, Martinez-Martin P. The Parkinson

anxiety scale (PAS): development and validation of a new anxiety scale. Mov Disord. 2014;29(8):1035–1043. doi:10.1002/mds.25919
39. Virmani T, Tizan S, Mazzoni P, Blair F, Greene PE. Motor fluctuations due to interaction between dietary protein and levodopa in Parkinson's disease. J Clin Movem Disord. 2016;3(8):1–9. doi:10.1186/s40734-016-0036-9
40. Cai T, Verze P, Bjerklund Johansen TE. The quality of life definition: where are we going? Uro. 2021;1(1):14–22. doi:10.3390/uro1010003
41. Revicki DA, Kleinman L, Cella D. A history of health-related quality of life outcomes in psychiatry. Dialog Clin Neurosci. 2014;16(2):127–135. doi:10.31887/DCNS.2014.16.2/drevicki
42. van Manen M. Phenomenology in its original sense. Quality Health Res. 2017;27(6):810–825. doi:10.1177/1049732317699381
43. Pardel-Dominguez L, Palmieri PA, Dominguez-Cancino KA, et al. The meaning of postpartum sexual health for women living in Spain: a phenomenological inquiry. BMC Pregn Childb. 2021;2(1):92. doi:10.1186/s12884-021-03578-y
44. Colaizzi PF. Psychological research as a phenomenologist views it. In: Valle RS, Mark K, editors. Existential-Phenomenological Alternatives for Psychology. New York: Oxford University Press; 1978. p. 48–71.
45. Picó C, Serra F, Rodríguez AM, Keijer J, Palou A. Biomarkers of nutrition and health: new tools for new approaches. Nutrients. 2019;11(5):1092–1122. doi:10.3390/nu11051092
46. Gershuni VM, Yan SL, Valentina Medici V. Nutritional ketosis for weight management and reversal of metabolic syndrome. Curr Nutr Reports. 2018;7(3):97–106. doi:10.1007/s13668-018-0235-0
47. Augustin KKA, Williams S, Eaton S, et al. Mechanisms of action for the medium-chain triglyceride ketogenic diet in neurological and metabolic disorders. Lancet Neurol. 2018;17:84–93. doi:10.1016/S1474-4422(17)30408-8
48. Basharat S, Bhatti A, Zia M, et al. Therapeutic effects of ketogenic diet components on Parkinson's disease. Asian J Allied Health Sci. 2019;3(4):56–63.
49. Cunnane S, Nugent SS, Roy M, et al. Brain fuel metabolism, aging and Alzheimer's disease. Nutrition. 2011;27(1):3–20. doi:10.1016/j.nut.2010.07.021
50. Phinney SVJ. The Art and science of low carbohydrate living: An expert guide to making the life-saving benefits of carbohydrate restriction sustainable and enjoyable. Vol. 1. Beyond Obesity LLC; 2011.
51. Batista P, Pereira A. Quality of life in patients with neurodegenerative diseases. J Neurol Neurosci. 2016;7(1:74):1–7. doi:10.21767/2171-6625.100074
52. Hashim SA, VanItallie TB. Ketone body therapy: from the ketogenic diet to the oral administration of ketone ester. J Lipid Res. 2014;55(9):1818–1826. doi:10.1194/jlr.R046599
53. Rana A, Qureshi A, Oghli Y, et al. Decreased sleep quality in Parkinson's patients is associated with higher anxiety and depression prevalence and severity and correlates with pain intensity and quality. Neurol Res. 2018;40(8):696–701. doi:10.1080/01616412.2018.1462880
54. Paoletti F, Farotti L, Parnetti L. Progression of symptoms in Parkinson's disease. Vol. 1. United Kingdom: Academic Press; 2020. (Martin CRP, V. R., editor. Diagnosis and Management in Parkinson's Disease: The Neuroscience of Parkinson's Disease).
55. Ohno K, Asammi M, Yoshihiko M. Is the default of 2 liters for daily per-capita water consumption appropriate? A nationwide survey reveals water intake in Japan. Japanese Water Health. London, UK 2018;16(4):562–573. doi:10.2166/wh.2018.281
56. Taylor MK, Swerdlow RH, Sullivan DK. Dietary neuroketotherapeutics for Alzheimer's disease: an evidence update and the potential role for diet quality. Nutrients. 2019;11(8):1910. doi:10.3390/nu11081910
57. Pinto A, Alessio Bonucci A, Maggi E, et al. Antioxidant and anti-inflammatory activity of ketogenic diet: new perspectives for neuroprotection in Alzheimer's disease. Antioxidants. 2018;7(63):1–16. doi:10.3390/antiox7050063
58. Maffoni M, Giardini A, Pierobon A, et al. Stigma experienced by Parkinson's disease patients: a descriptive review of qualitative studies. J Parkinson's Dis. 2017;2017:1–7. doi:10.1155/2017/7203259
59. Storoni M, Plant GT. The therapeutic potential of the ketogenic diet in treating progressive multiple sclerosis. Mult Scler Inter. 2015;2015:681289. doi:10.1155/2015/681289