

The ketogenic diet and MetSyn in Parkinson's disease – Symptoms, biomarkers, depression and anxiety: A case study



Author:

Melanie M. Tidman¹

Affiliation:

¹College of Graduate Health Studies, Faculty of Health Science, A.T. Still University, Mesa, United States of America

Corresponding author:

Melanie Tidman,
melanietidman@gmail.com

Dates:

Received: 22 Nov. 2023

Accepted: 26 Mar 2024

Published: 30 Apr. 2024

How to cite this article:

Tidman MM. The ketogenic diet and MetSyn in Parkinson's disease – Symptoms, biomarkers, depression and anxiety: A case study. J. metab. health. 2024;7(1), a93. <https://doi.org/10.4102/jmh.v7i1.93>

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The use of therapeutic carbohydrate restriction (TCR) in the form of a ketogenic diet (KD) in neurodegenerative disorders such as Parkinson's disease (PD) is increasing as an alternative treatment for primary and secondary symptoms. There exists a gap in the literature on symptoms of PD in the setting of metabolic syndrome (MetSyn) and possible comorbid impact on symptoms, biomarkers of health, cardiac risk, depression and anxiety. This case report documents a 24-week KD intervention for a 53-year-old man with multiple comorbid diagnoses, PD (Hoehn-Yahr stage IIa) with a history of morbid obesity with increased waist circumference, prediabetes, hyperinsulinaemia and significantly impaired mobility with chronic back pain, anxiety disorder and depression. Baseline cardiac risk ratios (CRR = triglycerides/HDL) were calculated and compared. The KD approach involved a well-formulated, ketogenic diet (fats 70%; protein 25%; carbohydrates 5% according to total daily energy intake for 24 weeks). Baseline, 12-week and 24-week biomarkers and scores on scales were compared. Clinically significant results were found when baseline biomarker results and scales were compared with 12-week results. Positive trends were seen for all variables at 24 weeks. Improvements in health biomarkers, including HbA1C, high sensitivity C-reactive protein (hs-CRP), triglycerides, fasting insulin, weight loss, waist circumference and cardiac risk were observed at 12 and 24 weeks. Some improvements in scores on an anxiety scale were seen. Based on our findings, KD is safe and effective for improving health biomarkers and symptoms of MetSyn, depression, anxiety and symptoms of PD. Future clinical trial studies for more generalisable results are needed.

Keywords: neurodegenerative disease; metabolic syndrome; obesity; low carb; ketogenic diet; symptoms; anxiety; depression; biomarkers; Parkinson's disease.

Introduction

In neurodegenerative diseases (NDDs) such as Parkinson's disease (PD), increasing research efforts have investigated the detrimental effects of oxidative stress, neuronal mitochondrial dysfunction and neuroinflammation on neuronal function and cognitive function.¹ The use of therapeutic carbohydrate restriction (TCR) in the form of a ketogenic diet (KD) to induce nutritional ketosis is increasingly being used to manage symptoms under investigation and to identify the potential application of nutritional ketosis in NDDs such as PD.²

Parkinson's disease has characteristic symptoms that are classified using a scale by Hoehn and Yahr.³ These symptoms and stages include:

- STAGE I: During this initial stage, the person has mild symptoms that generally do not interfere with daily activities. Tremor and other movement symptoms occur on one side of the body only. Changes in posture, walking and facial expressions occur.
- STAGE II: Symptoms start getting worse. Tremor, rigidity and other movement symptoms affect both sides of the body or the midline (such as the neck and the trunk). Walking problems and poor posture may be apparent. The person is able to live alone, but daily tasks are more difficult and lengthier.
- STAGE III: Considered mid-stage, loss of balance (such as unsteadiness as the person turns or when he or she is pushed from standing) is the hallmark. Falls are more common. Motor symptoms continue to worsen. Functionally the person is somewhat restricted in his or her daily activities now but is still physically capable of leading an independent life. Disability is mild to moderate at this stage.

- STAGE IV: At this point, symptoms are fully developed and severely disabling. The person is still able to walk and stand without assistance but may need to ambulate with a cane or walker for safety. The person needs significant help with activities of daily living and is unable to live alone.⁴

Current treatment for PD involves the use of a dopamine replacement in the form of Levodopa (L-Dopa) to address the motor symptoms associated with PD progression.⁵ Frequently, the non-motor symptoms associated with PD have a variable response to the administration of L-Dopa, calling for further investigation into alternative treatments to address these symptoms. Common non-motor symptoms include poor sleep quality, cognitive decline, behaviour changes, depressed mood, increased anxiety and a decrease in motivation to participate in social interactions.⁶ Patients with PD also often suffer from other comorbidities, which further interfere with functional independence and general health. Nutritional approaches through the application of the KD have suggested that the presence of blood ketones in the form of beta-hydroxy butyrate (BHB) can provide a feasible adjunctive treatment approach to address not only non-motor symptoms in PD but also associated metabolic health comorbidities.^{7,8}

By elevating ketones, a KD can provide an essential source of antioxidant fuels for neurons while reducing the production of reactive oxygen species.⁹ Nutritional ketosis is thought to mitigate neuronal mitochondrial dysfunction that occurs in many NDDs, such as PD, indicating a potential therapeutic effect in these disorders.¹⁰ Interventions targeting the elevation of BHB have been used to produce therapeutic benefits that were initially restricted to the treatment of neurological disorders such as epilepsy, but now increasingly used in NDDs like PD.

The influx of BHB and medium-chain fatty acids (MCFAs) can provide an alternative source of energy for the brain, resulting in a glucose-sparing effect within neuronal cells.¹¹ There is growing preclinical and clinical evidence that nutritional ketosis (BHB levels >0.5 mmol/dL) can mitigate some effects of oxidative stress, reduce mitochondrial dysfunction and improve central nervous system (CNS) metabolism through the reduction of inflammation in animals and humans.⁹

Metabolic syndrome (MetSyn) is a collection of symptoms including obesity, an increased waist circumference of greater than 101.6 cm in men (> 88.9 cm in women), elevated fasting blood sugar, elevated fasting insulin, high triglycerides and hypertension.¹ MetSyn can contribute to systemic inflammation and is associated with an increased risk of insulin resistance (IR), the development of type 2 diabetes and cardiovascular disease.^{1,12} Recent evidence suggests that IR may precede obesity rather than the converse because of inhibiting lipolysis and significantly increasing lipogenesis.^{13,14}

Insulin resistance can be related to carbohydrate intake, specifically those foods with a high glycaemic index and glycaemic load, stimulating a significant rise in blood glucose levels and consequently increasing insulin levels.¹³ Nutritional approaches that reduce high glycaemic carbohydrates can positively affect metabolic health conditions such as IR, prediabetes, type 2 diabetes and obesity. The use of KD resulting in nutritional ketosis (elevated blood ketones of >0.5 mmol/L) is also a valuable intervention strategy for chronic conditions such as epilepsy and NDDs² with improvements in several cardiovascular risk parameters such as triglycerides, HDL and HbA1C.¹⁵

This case study involves a 53-year-old man with Hoehn and Yahr (H-Y) stage IIa PD, morbid obesity (Class III), MetSyn, symptoms of depression and anxiety, abnormal levels of seven biomarkers, elevated cardiac risk and chronic pain with significantly impaired mobility. The participant reported symptoms of PD, including freezing gait, tremors in upper extremities interfering with activities of daily living (ADLs), poor sleep quality, depression, anxiety, cognitive decline in short-term memory and bradykinesia. These symptoms are consistent with Stage IIa, which the patient's neurologist confirmed on the signed permission form at baseline. The question under consideration is: How does TCR by consuming a KD affect PD symptoms, biomarkers, obesity, cardiac risk, depression and anxiety after 24 weeks? This case study was approved by the Institutional Review Board at A.T. Still University, Study Protocol #2020-058.

Case presentation

Baseline medications, comorbidities and functional impairments

At baseline our subject with PD and MetSyn also reported sleep apnoea (on continuous positive airway pressure therapy), chronic insomnia (only sleeping 4–6 h per night), chronic hamstring tendonitis, back pain, chronic anxiety and obsessive-compulsive disorder (OCD), gait abnormalities (walks bent over greater than 45° at the waist using a walker for less than 3.28 m because of significant truncal weakness), heart palpitations, prediabetes and depression. Medications include paxil (for anxiety), sinaproxen (for pain), pramipexole (PD medication), cyclobenzaprine (for pain), celebrex (for pain) and melatonin (3 mg) for chronic insomnia. The subject spends most of the day in bed because of pain and fatigue and cannot go outdoors as a result of mobility impairments. The subject reports that health visits with primary care physicians and neurologists were often conducted over telehealth because of limited mobility. The subject reports a diminished quality of life and an inability to participate in activities with his 18-year-old son. He also requires in-home assistance for all activities of daily living. The subject used to be a chef and an avid gardener and could no longer work in the kitchen or his yard. He reported at baseline that his daily pain level ranges between 8 and 10/10 using a visual analogue scale (VAS).

Baseline biomarker and functional levels

Baseline blood work revealed significantly abnormal levels of the following biomarkers: fasting insulin = 206.94 pmol/L, HbA1C 40 mmol/mol, hs-C-reactive protein (hs-CRP) 2.87 mg/L, with a cardiac risk ratio (triglycerides/HDL) = 0.50 mmol/L. Baseline weight was 138.35 kg, with a baseline waist circumference of 154.9 cm. Our subject reported that at baseline, his PD symptoms were increasingly problematic, mobility was limited and his diet comprised highly processed foods, fast foods and high sugar intake, stating his sugar consumption was 'out of control'.

Methods

The subject was consented at baseline during a 2-h Zoom appointment, and KD methods were explained. The use of a telemedicine approach through a Zoom Live meeting platform in the case of this case study in the management of PD has increased since the coronavirus disease 2019 (COVID-19) pandemic of 2020. Because the case study was conducted during the 2020 pandemic, it was necessary to use a telemedicine approach for the assessment of the participant. According to Cubo et al. (2022), 'A growing body of evidence supports the feasibility and effectiveness of telemedicine tools for PD and other movement disorders' (pg1). The authors found that although there are challenges with the use of telemedicine approaches, outcomes and variables can be effectively assessed with good results regarding satisfaction and positive results in clinical care education, research applications and treatment.¹⁶ The patient's neurologist verified PD diagnosis in a written communication at baseline.

The nutrition plan included 70% – 75% fats, 20% – 25% protein and 5% – 10% carbohydrates according to total daily caloric intake. These dietary levels are similar to interventional macronutrient limits from a study by Phillips et al. (2019)² and by Tidman et al.^{8,17}. Protein requirements were set between 0.8 and 1.0 g/kg of body weight to preserve L-dopa absorption, avoiding high protein intake, which could exacerbate symptoms of dyskinesias in some persons with PD.¹⁸ Educational materials were provided, including a recommended food list and a 100-page cookbook with recipes and meal plans.² Over the 24 weeks, the subject's diet consisted of meats, fish, poultry, eggs and low-glycaemic vegetables.

Training on using a daily blood glucose/ketone metre was provided at the baseline appointment, along with a free KetoMojo Blood Glucose/Ketone meter for testing fasting blood glucose and blood ketone levels at home. The subject was encouraged to test his fasting blood glucose and ketones daily one hour after awakening to support evidence of dietary consistency, aiming for fasting blood glucose below 5.55 mmol/L (100 mg/dL) and blood ketones between 0.5 mmol and 3.0 mmol/L.¹² Blood glucose and ketone logs were emailed to the study researcher to note dietary compliance and levels of nutritional ketosis.

During the baseline appointment, the subject was emailed for baseline bloodwork, a Parkinson's Anxiety Scale (PAS) and a Center for Epidemiologic Studies Depression Scale-Revised-20 (CESDR) to fill out and return via email or US mail. The United Parkinson's Disease Rating Scale (UPDRS) Parts I and II were also provided to enable him to report current non-motor symptoms related to his PD. The subject reported his weight and waist measurement and answered questions about his daily activities and routines. Zoom live meetings were held as often as the subject requested, and email communication was used weekly or more frequently as needed to answer questions or clarify the food lists or meal plans.

The CESDR¹⁹ is a depression symptom self-assessment with 20 questions scored using a Likert-type scoring approach. Total CESDR scores are calculated by finding the sum of the self-scored 20 questions. A score at or above 16/60 indicates a person is at risk of clinical depression.¹⁹ The CESD-R-20 scores responses to questions such as 'I was bothered by things that don't usually bother me', 'I did not feel like eating', 'I felt I could not shake off the blues', etc. The subject's responses were scored using a 1–4 Likert-type scale, which indicated 1 = rarely or none of the time (less than 1 Day), 2 = some or a little of the time (1–2 Days), 3 = occasionally or a moderate amount of the time (3–4 Days) and 4 = most or all of the time (5–7 Days).¹⁹

The PAS is a 12-question scale with Likert-type, self-scored responses between 1 and 5 for each question.²⁰ The PAS contains questions such as 'Feeling Anxious or Nervous', 'Feeling tense or stressed', 'Being unable to relax', 'Excessive worrying over everyday matters', etc. The PAS uses a 5-point Likert-type scale of 0 – not at all, 1 – very mild, 2 – sometimes, 3 – moderate, 4 – severe.²¹

The UPDRS contains four main parts, which are:

- Part I: Non-motor Symptoms of Mentation, Mood and Behaviour
- Part II: Activities of Daily Living
- Part III: Motor Examination
- Part IV: Complications of Therapy.²²

Parts I and II scores were obtained and reviewed for this case study. Part I scores were based on four questions involving symptoms associated with intellectual impairment, thought disorder, depression and motivation, with possible response scores of 0–4 using a Likert-type scale. The UPDRS-Part II section comprised 13 questions scored 0–4 for each item involved with activities of daily living. These questions involved symptoms related to scores on the following subtests: speech, salivation, swallowing, handwriting, cutting food, dressing, hygiene, turning in bed, falling, freezing with gait, walking, tremors and sensory complaints.²²

Ethical considerations

All aspects of this case study, including participant recruitment, study design, methods, data collection strategies

and data analysis, were subject to ethics review and oversight by the Institutional Review Board of A.T. Still University (Protocol #2020-058). Mesa, Arizona. The study is registered with ISRCTN #80586209.

Results

Biomarkers of health

The subject's biomarker testing revealed significant changes in some health biomarkers over 24 weeks, including reductions in weight (-28 kg, for a BMI of 32.9 kg/m² down from 41.4 kg/m²) and waist circumference (114.3 cm) down from 154.94 cm for a loss of 40.64 cm. HbA1C (-[39 mmol/mol] triglycerides [0.61 mmol/L], fasting insulin - [76.40 pmol/L] and the calculated cardiac risk ratio [triglycerides/HDL][0.36 mmol/L]) all improved at 24 weeks (Table 1). Readings for hs-CRP reduced significantly at 12 weeks (-13.40 mg/L) but increased at 24 weeks (+19.30 mg/L). The subject reported he had an upper respiratory infection during his 24-week bloodwork, which may account for a slight increase in his hs-CRP value.

The subject self-assessed daily dietary compliance by testing blood glucose and ketones to support the contents of his submitted food diaries. This was revealed through weekly submitted glucose/ketone logs, showing that the subject maintained ketone levels consistent with nutritional ketosis over the 24 weeks (> 0.5 mmol/L).

The United Parkinson's Disease Rating Scale

The subject reported improvements in Part I and Part II UPDRS scores for non-motor symptoms of PD, including slightly improved mentation, mood and behaviour (Part I) and activities of daily living (ADL) (Part II). The subject's baseline UPDRS- Part I score was 2/16, indicating a few negative symptoms associated with mentation, mood and behaviour. The subject's baseline Part II total score was 15/52, indicating mild to moderate symptoms related to activities of daily living. At baseline, the subject had very limited mobility and could only walk 3.045 m – 3.65 m to his bathroom using a front-wheeled walker. The subject's 24-week Part II Scores for ADLS revealed slight improvements, including scores for speech, swallowing, handwriting, self-feeding, dressing, hygiene,

falling, freezing, walking, tremor and sensory impairments at baseline, scoring 11/52. The subject reported his walking had improved after 24 weeks to the point where he could walk with a walker around his yard, and he could go to a local gym to exercise with his son 2–3 days a week, whereas, at baseline, he was in bed most of the day. The subject also reported significant reductions in chronic back pain and was able to discontinue two of his three pain medications after contacting his physician for a weaning protocol. He noticed that after 24 weeks, his daily pain levels were between 1 and 3/10, down from a baseline daily reported pain level of 8/10 (VAS).

Depression scale: The centers for epidemiologic studies depression scale revised (CESD-R-20)

The subject's baseline score on the CESD-R-20 was 38/60, indicating moderate symptoms of depression. No improvements were seen in depression scores at 24 weeks, with a final score of 37/60.

Anxiety scale: The Parkinson's anxiety scale

The subject's baseline total score on the PAS was 31/60, indicating moderate symptoms of anxiety. Some mild improvements were observed over the 24 weeks for scores of anxiety-related symptoms, with a final score of 24/60 (see Table 1 for baseline, 12 and 24-week results for all variables).

Discussion

Ketogenic diet can result in improved or preserved brain function and enhanced neuronal survival.² This result suggests the application of KD to achieve nutritional ketosis may have considerable therapeutic potential in treating the glucose hypometabolism often associated with NDDs such as PD and neuropsychiatric disorders.¹⁰ The case study revealed improvements at 24 weeks in scores on an anxiety scale and symptoms of PD with additional improvements in biomarkers of health, including weight loss, triglycerides/HDL, fasting insulin and HbA1C consistent with studies by Tidman et al. (2022) and Bhuiyan et al. (2021)

There was substantial weight loss after the initial 12 weeks (16.83 kg), with an overall weight loss of 28.12 kg at the 24-week mark (Table 1). Kraeuter et al. (2019) found that fat

TABLE 1: Baseline, 12-week and 24-week results: All variables (raw scores).

Biomarker	Baseline results	Post 12 weeks study results	12-week change	Post 24 weeks results	24-week change
Triglycerides (mmol/L)	0.78	0.71	-0.07	0.61	-0.17
HDL (mmol/L)	1.5516	1.6292	+0.0776	1.655	+0.1034
HbA1C (mmol/mol)	40	37	-3	39	-1
hs-CRP (mg/L)	28.7	13.40	-15.30	40.80	+19.30
Insulin (pmol/L)	206.96	52.78	154.18	76.40	-130.8
Weight (kg)	138.35	121.52	-16.83	110.04	-28.3
BMI (kg/m ²)	41.4	35.1	-6.3	32.9	-8.5
Cardiac risk ratio (Trigs/HDL) (mmol/L)	0.50	0.43	-0.07	0.36	-0.14
Waist measurement (cm)	154.94	135.89	-19.05	114.3	-40.64
PAS	31/60	21/60	-10	24/60	-7
CESDR	38/60	41/60	+2	37/60	-1
UPDRS Pt I	2/16	2/16	0	2/16	0
UPDRS Pt II	15/52	10/52	-5	11/52	-4

consumption and the incidence of obesity are inversely related, while carbohydrate consumption was directly correlated with obesity.²³ In addition, KD is frequently shown to reduce hunger and increase satiety^{24,25,26} (also reported by our case study subject), resulting in weight loss in obese individuals. In contrast, before the study, our subject felt like snacking all day long because of feelings of hunger. Similar to our case study, other studies found significant weight loss, improved satiety and improved glucose control with KD.⁸

According to Leehey et al. (2017), persons with PD who also met the criteria for metabolic syndrome tended to have a more rapid progression in their PD symptoms over time as measured by the UPDRS when compared with those who did not have metabolic syndrome as a comorbidity. In addition, recent studies have demonstrated weight loss improves metabolic health, improves IR, reduces the symptoms of MetSyn and has the potential to slow the progression of PD over time with improvements in both non-motor and motor scores (UPDRS) when compared with patients with poor metabolic health.^{8,27,28} Our case study subject began the study period with symptoms of MetSyn. As a result of the KD intervention, our subject had improvements in fasting insulin and waist circumference, BMI, hypertension, fasting glucose (HbA1C) and a slight improvement in triglycerides and HDL.

Pico et al. (2019) provide a foundation for testing biomarkers (HbA1c, triglycerides, hs-CRP, fasting insulin, HDL) in this case report. Our analysis of biomarkers after 24 weeks revealed improvements in almost all biomarkers with reductions in inflammatory markers (hs-CRP), triglycerides, fasting insulin and improved HDL. These case study results are consistent with studies by Pico et al. (2019) and Phillips (2019), who found significant improvements in biomarkers associated with cardiovascular risk calculated by triglycerides/HDL.^{29,30,31} Our subject's TG/HDL ratio revealed a decreased risk of a potential future cardiac event at 24 weeks.

In a systematic review by Dewsbury et al. (2021), the authors addressed the problems associated with diminished or disordered glucose metabolism in the brain, which often precedes any clinical symptoms of depression or anxiety that can be associated with NDDs.¹¹ An overall analysis of 17 study articles revealed that through the use of KD, which induced therapeutic nutritional ketosis and elevation of blood ketones level (<0.5 mmol/L) through both dietary interventions and the application of exogenous ketone supplements, improvements were found in cognitive measures, brain ketone utilisation and general health.¹¹ The Dewsbury et al. (2021) systematic review supports the use of KD for producing positive effects on brain function, psychiatric disorders and general health, which are foundations for this case report. In addition, positive changes were seen in our subject at 24 weeks on the UPDRS Part I scores for the subtests mentation, mood and behaviour.

These findings by Dewsbury et al. (2021) are consistent with the results of our case study subject, who reported modest improvements in his general mood, motivation to participate again in daily activities and social situations and improved sleep quality over the 24 weeks. Furthermore, clinical research studies on blood ketones support our findings of improved cognitive function and motivation,³² reduced PD symptoms, improved pain and mood³³ and decreased nighttime urinary frequency.³⁴

In addition, KD may help to treat some symptoms of PD with primary effects on reducing oxidative stress and mitochondrial dysfunction, which frequently cause neuroinflammation and widespread neuronal dysfunction.^{10,35} Ketogenic diet can result in the elevation of blood ketones, which can provide an alternative fuel source for neuronal cells in an environment of glucose restriction. Our subject was able to maintain BHB levels consistent with nutritional ketosis throughout the 24 weeks of the study and reported enhanced mood, motivation, sleep quality and reduced levels of anxiety. Therefore, KD can positively influence brain energy utilisation with reduced inflammation, improved mood and enhanced cognition.^{2,8}

Some of the limitations of a case study include the small sample size ($n = 1$), non-generalisable results, a lack of statistical analysis and possible placebo effects influencing the subject's responses on the UPDRS, anxiety and depression scales. Nutritional studies have inherent issues with the validity of food tracking and integrity of dietary compliance, even though we attempted to control for this using daily blood glucose/ketone readings and the MyFitnessPal app completed after each meal daily for more immediate recall. Zoom appointments have inherent limitations in terms of a lack of face-to-face contact, which may have altered results. In addition, we cannot deny the possible benefits of weight loss apart from the independent effects of the KD intervention for improving symptoms of PD and biomarkers.

Conclusions

The applications of dietary interventions in PD are increasingly of research interest. Improving outcomes for patients with PD through nutritional approaches can augment medication management to promote improvements in symptoms and general health. This case study demonstrates that empowering individuals with PD to take control of their health and providing them with nutritional strategies can improve outcomes over time. In addition, our case study subject reported reduced non-motor symptoms of PD, and biomarker laboratory results and commonly used anxiety and depression scales indicated a reduction of the risks associated with comorbidities such as MetSyn, anxiety and depression. The results of this case study reveal the need for more randomised clinical trials to test further the associations of nutritional ketosis and the use of the KD for symptom management, and the level of carbohydrate restriction needed for improving cognition, reducing symptoms of PD, depression, anxiety and benefits to overall health.

Acknowledgements

The author would like to sincerely thank and acknowledge the ongoing support of the Colorado Parkinson Foundation and their Board of Directors. Their commitment to research efforts is greatly appreciated. In addition, a sincere thank you to the IRB of A.T. Still University for support and oversight of this research.

Competing interests

The authors declare that they have no financial or personal relationship(s) that may have inappropriately influenced them in writing this article.

Author's contributions

The primary author was responsible for all aspects of study and methods design, data collection, data analysis, manuscript preparation and oversight of this research.

Funding information

The Colorado Parkinson Foundation covered the participant's study-related costs. The author did not receive any funds for the creation or oversight of any procedures associated with this case study.

Data availability

The data that support the findings of this study are available on request from the corresponding author (M.M.T.).

Disclaimer

The views and opinions expressed in this article are those of the authors and do not necessarily reflect the official policy or position of any affiliated agency of the authors.

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