NUTRITIONAL KETOSIS AS A NOVEL THERAPEUTIC STRATEGY TO STABILIZE CHRONIC AORTIC DISSECTION IN MARFAN SYNDROM

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Protocol Revision History

Initial Approval Version	**17 Oct 2025**

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1.0 Synopsis

Title:	Nutritional Ketosis as a Novel Therapeutic Strategy to Stabilize Chronic Aortic Dissection in Marfan Syndrome
Study Description:	Patients with Marfan syndrome who have chronic or residual aortic dissection remain at ongoing risk for progressive aortic dilation and eventual need for operative repair. Despite advances in antihypertensive therapy and open/endovascular/hybrid techniques, no medical therapy has been shown to slow aortic enlargement once chronic dissection is established. But promising results have been demonstrated in rodent studies utilizing ketogenic dietary interventions. Therefore, this prospective, single-arm, intent-to-treat pilot clinical trial will test the feasibility, safety, and potential efficacy of inducing and maintaining nutritional ketosis in patients with Marfan syndrome and chronic aortic dissection
Objectives:	Primary Objective: • To test the feasibility, safety, and potential efficacy of inducing and maintaining nutritional ketosis in patients with Marfan syndrome and chronic aortic dissection (Prior type A dissection with residual distal dissection or Stanford Type B; and a maximal aortic diameter 4.0-5.0 cm). Secondary Objective: • Observation of changes related to aortic dissection and inflammatory markers • Patient adherence to ketogenic dietary recommendations
Endpoints:	Primary Endpoint: • Freedom from aortic intervention at 12 months compared with historical controls. Secondary Endpoints: • Change in aortic diameter • Growth rate • Systemic inflammatory markers • Dietary adherence metrics
Study Population:	15 patients- Prospective Cohort 15 patients- Historical Control
Phase:	N/A
Description of Sites / Facilities Enrolling:	Washington University School of Medicine / Barnes-Jewish Hospital

Description of Study Intervention:	A study coordinator and dietitian will provide remote counseling and compliance support. Ketosis will be quantified by β-hydroxybutyrate levels from finger-stick meters (self-reported through a secure cloud-based portal) and validated with serum assays every 3 months. Standard-of-care CT angiography will be obtained at baseline, 6, and 12 months to assess aortic diameter, false-lumen status, and remodeling. All participants will continue optimal antihypertensive and impulse-control therapy under cardiovascular supervision.
Study Duration:	Estimated time (in months) from when the study opens to enrollment until completion of data analyses: 24

2.0 Introduction

2.1 Background

People with Marfan syndrome are born with a change in a gene that makes the walls of their blood vessels weaker than normal. One of the most serious problems caused by Marfan syndrome is a tear in the aorta (aortic dissection), the large blood vessel that carries blood from the heart to the rest of the body. When a tear occurs in the first part of the aorta (type A dissection), emergency surgery is necessary. When a tear occurs further down in the aorta (type B dissection), optimal medical therapy is most often prescribed. When a residual or chronic aortic dissection is present after the acute dissection, the aortic wall is weaker than normal. Over time, this weakened part of the aorta can slowly stretch and grow larger. If the aorta keeps expanding, patients may eventually need a major operation to repair it.

Currently, the only way to manage the condition of a chronic aortic dissection is with medicines that lower blood pressure and heart rate. These treatments reduce stress on the aorta but do not stop the aorta from getting bigger. There is no medical therapy known to slow or stop aortic growth once a dissection has already happened.

In recent animal studies, it was found that when the body uses ketones – natural molecules made during a ketogenic diet – the blood vessels become less inflamed and more stable. The ketogenic diet is a high-fat, very-low-carbohydrate eating plan that has been safely used for many years to treat children with epilepsy. In animals, nutritional ketosis reduced vessel wall injury and limited the growth of aneurysms.

In this pilot clinical trial, we will test whether a carefully supervised ketogenic diet can safely help people with Marfan syndrome who already have a chronic or residual aortic dissection. Fifteen participants will work with a study coordinator and dietitian to learn how to follow the diet and will have regular guidance and check-ins. They will measure their blood ketone levels at home with a simple finger-stick device and relay their readings to the research team. Every three months, blood samples will also be collected to confirm the body's level of ketosis.

Participants will continue their usual heart and blood-pressure medicines and regular visits with their doctors. CT scans of the aorta will be performed at the start of the study and then again at 6 and 12 months to see if the aorta changes in size.

The main goal is to see how many patients can avoid needing aortic surgery within one year, compared with what is normally expected from past studies. We will also track how well patients follow the diet, how their aorta changes, and whether inflammation in their blood decreases.

If this approach proves safe and effective, it could become the first medical treatment aimed at stabilizing the aorta in Marfan syndrome, reducing the need for major operations and improving long-term health for people living with this genetic condition.

2.2 Study Rationale

Chronic aortic dissections in Marfan syndrome represent a particularly challenging form of genetically triggered aortopathy.[1-3] Despite meticulous impulse-control therapy with beta-blockers and angiotensin receptor blockers (ARBs), a large proportion of patients experience progressive thoracoabdominal aortic dilation and false-lumen expansion.[2,4,6] Over time, these changes predispose to rupture, malperfusion, or the need for extensive aortic repair, all of which carry substantial morbidity.[7-9] Current medical therapies target hemodynamic stress as supportive therapy but do not address the molecular drivers of wall degeneration such as oxidative injury, smooth muscle cell apoptosis, and extracellular matrix breakdown.[2,10]

Preclinical data from our group and others demonstrate that nutritional ketosis – a physiologic metabolic state induced by carbohydrate restriction or exogenous ketone supplementation – attenuates these same degenerative mechanisms (see Figure 1).[11,12] In murine aneurysm and dissection models, ketogenic interventions significantly reduced macrophage infiltration, matrix metalloproteinase activity, and extracellular matrix degradation, while improving vascular smooth muscle cell viability and reparative aortic wall collagen content.[13] Collectively, these effects promote greater structural stability and reduced inflammatory remodeling.[14]

This biologic rationale, combined with the extensive clinical safety record of ketogenic therapy in epilepsy and metabolic syndrome, provides a strong foundation for translation to aortic disease.[12,15-18] Importantly, Marfan aortopathy is characterized by heightened transforming growth factor-β signaling and impaired extracellular matrix turnover, both of which are influenced by cellular redox balance and energy metabolism – pathways we have previously shown to be modulated in the aortic wall by ketone bodies such as β-hydroxybutyrate.[13,19-21] Thus, introducing a ketogenic intervention into this population could yield not only clinical benefit but also mechanistic insight into how metabolic modulation impacts connective tissue integrity in the setting of Marfan syndrome.

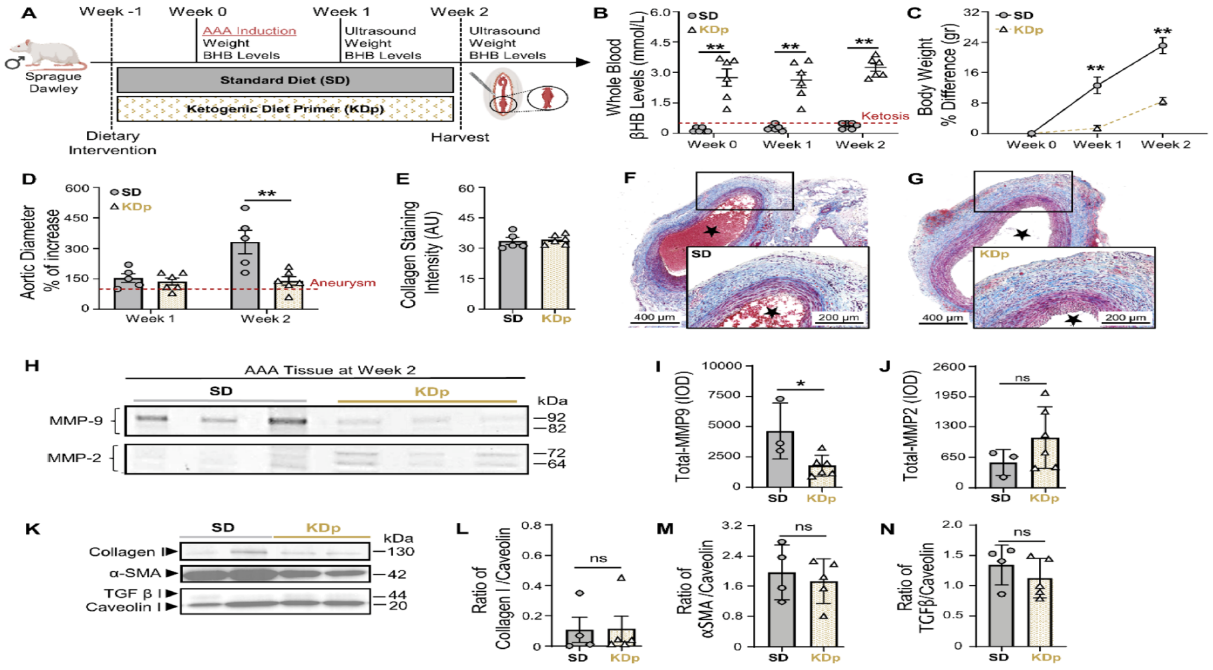

Figure 1. Ketogenic Diet Reduces Aortic Aneurysm Expansion in Rodent Model. *(published in: Sastriques-Dunlop S, et al. Sci Rep 2024; **14**(1): 1438) Ketosis attenuates AAA formation and MMP9. (A) Rats underwent exposure to PPE for AAA creation. The experimental group was given a ketogenic diet that started one-week prior to PPE exposure (KDp; N = 6) while the control group was fed a standard chow diet (SD; N = 5). (B) Ketosis (βHB whole blood levels > 0.5 mM/L) was verified at week 0, 1 and 2 in SD (0.2±0.1, 0.3±0.1 and 0.4±0.1) and KDp rats (3±1, 3±1 and 3±0.5) respectively (p < 0.01). (C) Percent body weight difference in SD versus KDp rats at week 1 (13±5 vs. 2±1.3) and at week 2 (23±5 vs. 8±2) respectively (p < 0.001). (D) Percent aortic diameter in SD versus KDp rats at week 1 (154±48 vs. 137±42; p = ns) and at week 2 (332±129 vs. 140±152; p = 0.008) respectively (aneurysms were defined by a >100% increase in the aortic diameter compared with pretreatment measurements). (E) AAA collagen staining quantification for SD and KDp at week 2 (33±4 vs. 34±2; p = ns) respectively. (F and G) Trichrome staining of abdominal aortas (cross-section of tissue slides) with 5x magnification for SD and KDp rats. Areas with blue staining signify areas with higher collagen deposition. (H) Zymogram demonstrating total MMP9 and MMP2 levels were measured by integrated optical density (IOD). (I) Total MMP-9 levels for SD and KDp at week 2 (4.6±2 x 10^3 vs. 1.7±0.8 x 10^3; p = 0.02) respectively. (J) Total MMP-2 levels for SD and KDp at week 2 (5.4±3 x 10^2 vs. 1±0.6 x 10^3; p = ns) respectively. (K) Representative western blots of collagen 1, α-SMA, TGFβ-1 and Caveolin 1 in AAA tissue. (L) Collagen I protein content expressed as a ratio to Caveolin 1 content in AAA tissue of SD and KDp rats (0.1±0.1 vs. 0.1±0.1 respectively; p = ns). (M) α-SMA protein content expressed as a ratio to Caveolin 1 content in AAA tissue of SD and KDp rats (2±0.7 vs. 1.7±0.6 respectively; p = ns). (N) TGFβ protein content expressed as a ratio to Caveolin 1 content in AAA tissue of SD and KDp rats (1.3±0.3 vs. 1.2±0.3 respectively; p = ns).*

2.3 Risks and Benefits

Risks: Although a well-formulated ketogenic diet is generally safe for most individuals when properly supervised, potential risks include dehydration, electrolyte imbalances (particularly low sodium, potassium, or magnesium), and transient increases in serum lipids during the early adaptation phase. Some participants may experience gastrointestinal discomfort, fatigue, or headache - collectively known as "keto flu" - during the first few weeks of dietary transition. In rare cases, prolonged ketosis can exacerbate preexisting hepatic or renal dysfunction or cause elevations in uric acid. For patients with cardiovascular disease, monitoring of lipid profiles and metabolic parameters is needed. To minimize these risks, participants in this study will undergo regular laboratory evaluations, receive individualized dietary guidance from the research team and dietitian, and remain under medical supervision

throughout the intervention period

The research blood draws performed have a minimal risk of pain, bruising or the feeling of lightheadedness at the time of the blood draw.

Patient PHI will be recorded, used and stored during the course of this study, thus there is a potential risk of participant loss of confidentiality. All data will be recorded, stored, and analyzed using hospital computers on the virtual desktop servers in order to minimize the risk of a breach.

Benefits: There is a potential benefit that the ketogenic dietary interventions implemented may help delay the need for aortic repair. Patients will continue standard of care CT imaging for monitoring, and all clinical decisions will be made in accordance with the current standard of care.

3.0 Objectives and Endpoints

Objectives	**Endpoints**
Primary	
Test the feasibility, safety, and potential efficacy of inducing and maintaining nutritional ketosis in patients with Marfan syndrome and chronic aortic dissection	Freedom from aortic intervention at 12 months compared with historical controls.
Secondary	
Observation of changes related to aortic dissection and inflammatory markers Patient adherence to ketogenic dietary recommendations Explore the mechanistic relationship between circulating ketone levels, systemic inflammation, and aortic remodeling as measured by imaging and biomarker assays	Change in maximal descending thoracic aortic diameter and annualized growth rate Degree of false-lumen thrombosis Correlation between serum β-hydroxybutyrate levels and aortic remodeling using finite-element imaging analysis Changes in systemic inflammatory and metabolic biomarkers Overall diet adherence and safety.

4.0 Study Population

4.1 Inclusion Criteria

1. Adults between 18 and 50 years old.
2. Ability to understand and willingness to sign an IRB approved written informed consent document.
3. Genetically or clinically confirmed Marfan syndrome

4. Chronic descending thoracic aortic dissection present for at least three months
5. Maximal descending thoracic aortic diameter must measure between 4.0 and 5.0 cm at baseline on contrast-enhanced CT angiography (CTA)
6. Have been clinically stable and consistent antihypertensive regimen for at least four weeks

4.2 Exclusion Criteria

1. Acute or rapidly enlarging dissection (>0.5 cm increase over the preceding three months)
2. Prior descending thoracic aortic repair or endograft placement
3. Advanced renal or hepatic dysfunction
4. Poorly controlled diabetes requiring insulin
5. Active malignancy, pregnancy, or other metabolic or nutritional disorders that would contraindicate ketogenic therapy
6. Body mass index below 18 kg/m^2
7. Inability to comply with dietary restrictions or follow-up imaging
8. Current enrollment in another interventional study, which in the opinion of the PI, may confound study results.
9. Patients who, in the opinion of the PI, are not suitable candidates for study participation.

4.3 Historical Control Cohort

Historical control data will be collected from previously published Marfan dissection cohorts, where approximately 20-25% of patients progress to intervention during the first year of follow-up.[2,3]

6.0 Study Interventions

6.1 Study Procedures

Participants will initiate a supervised ketogenic diet formulated to provide approximately 70-75% of calories from fat, 20% from protein, and less than 10% from carbohydrates, consistent with protocols successfully used in therapeutic epilepsy trials but adapted for adult cardiovascular patients.[12,16,24,25] Caloric intake will be individualized to maintain stable weight and adequate micronutrient balance. Each participant will receive an orientation session with a registered dietitian, followed by weekly virtual or phone check-ins for the first month and bi-weekly thereafter. Educational materials, individualized meal plans, and recipes will be provided.

To ensure safety and adherence, participants will use a handheld ketone meter (Keto-Mojo) to measure β-hydroxybutyrate levels three times per week via saliva as well as finger-stick blood testing.[26,27] These readings will be automatically uploaded to a secure, HIPAA-compliant cloud platform monitored by the study team. Serum ketone validation and metabolic panels, including electrolytes, lipid profiles, and liver function tests, will be obtained at baseline and every three months. A study coordinator will review adherence data weekly and contact participants who fall below target ketosis thresholds (≥0.5 mmol/L). Blood pressure logs and medication compliance will be reviewed at each visit to ensure consistent impulse control (see

Table 1).

Imaging assessments will be performed using standard-of-care CTA at baseline, 6, and 12 months. All studies will follow an institutional low-radiation surveillance protocol optimized for chronic dissection.[2-4] Measurements will include maximal descending thoracic diameter, true and false lumen cross-sectional areas, and extent of thrombosis.[4,23] Each scan will be reviewed by two blinded imaging readers to minimize measurement bias.

Participants will remain under the care of their treating cardiovascular physicians throughout the study, ensuring continuation of best-practice medical management. Any indication for surgical or endovascular intervention during the trial will be determined by the treating team using standard clinical criteria, and the patient will be considered to have reached the primary study endpoint.

Table 1: Schedule of Activities

Assessment / Measurement	Baseline	Month 3	Month 6	Month 9	Month 12
Clinical Evaluation	✓	✓	✓	✓	✓
Dietitian / Coordinator Visit	Weekly (Month 0–1), then bi-weekly	✓	✓	✓	✓
Home β-Hydroxybutyrate (Finger-Stick Meter)	Ongoing, ≥3× per week	Continuous	Continuous	Continuous	Continuous
Serum β-Hydroxybutyrate & Metabolic Panel	✓	✓	✓	✓	✓
Inflammatory Biomarkers (hs-CRP, IL-6, etc.)	✓	–	✓	–	✓
Fasting Lipids, HbA1c, Glucose	✓	–	✓	–	✓
Body Weight / BMI	✓	✓	✓	✓	✓
Blood Pressure & Pulse Logs	Continuous (weekly)	Continuous	Continuous	Continuous	Continuous
CT Angiography of Thoracic Aorta	✓	–	✓	–	✓
Adverse Event Review & Safety Labs	✓	✓	✓	✓	✓
Diet Adherence Assessment	✓	✓	✓	✓	✓

Notes:
- ✓ indicates a scheduled assessment
- Continuous activities (home ketone testing, BP logs) are ongoing throughout the study.
- All CTAs follow low-radiation, contrast-enhanced dissection surveillance protocols.
- Data from serum assays, imaging, and clinical monitoring will be integrated for correlation analyses between ketosis level, inflammation, and aortic remodeling.

6.2 Duration of Participation

The duration of active research participation is 12 months. Participants will remain under the care of their treating cardiovascular physicians throughout the study, ensuring continuation of best-practice medical management. Any indication for surgical or endovascular intervention during the trial will be determined by the treating team using standard clinical criteria, and the patient will be considered to have reached the primary study endpoint.

7.0 Regulatory and Reporting Requirements

The entities providing oversight of safety and compliance with the protocol require reporting as outlined below.

7.1 Unanticipated Problems and Adverse Event Reporting

Adverse events will be tracked from the time of the baseline visit until the 12 Month visit. Only events that are considered at least possibly related to participation in this study will be recorded on the AE case report form.

7.2 WU PI Reporting Requirements

The study principal investigator and study coordinator will monitor for breaches of confidentiality and other adverse events on an ongoing basis. Once the PI or study coordinator becomes aware of a reportable adverse event, the event will be reported to HRPO according to institutional guidelines.

Protocol and/or consent revisions will be submitted to HRPO and approved prior to being implemented.

Pre-approval of all protocol exceptions must be obtained prior to implementing the change.

8.0 Data Collection and Security

The names of patients enrolled in the study will be recorded on an enrollment log that will include the participant's name and an assigned study ID. Additional data from the patient's medical record will be collected, such as age, sex, comorbidities, etc.

The handheld ketone meter (Keto-Mojo) readings will be automatically uploaded to a secure, HIPAA-compliant cloud platform monitored by the study team.

Study data will be stored and analyzed on a password protected, encrypted device. Only approved study personnel will have access to subject information. No subject PHI will be shared outside of the approved study personnel

9.0 Data Safety and Monitoring

The study Principal Investigator and Research Patient Coordinator will monitor for any safety concerns on an ongoing basis. Any symptomatic hypotension, electrolyte disturbance, or weight loss exceeding 10% of baseline will prompt protocol review and dietary adjustment by the study team.[24,25] Should the principal investigator or designee become aware of any breach of confidentiality, or adverse event, the event will be reported according to institutional guidelines as outlined above, in Section 7.0

10.0 Statistical Considerations

All analyses will follow an intent-to-treat principle. Continuous variables will be summarized as mean ± standard deviation, with within-subject changes analyzed using repeated-measures mixed-effects models. Dichotomous outcomes will be reported as proportions with 95% confidence intervals. The feasibility benchmark for success will be defined as at least 80% participant retention and 70% adherence to target ketosis levels across the study period

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