Proposal: Assessing the Impact of the Ketogenic Diet in Adults with stage IV Colon cancer on First Line Chemotherapy

by

Danielle Hill, RD, LDN, CSO

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Mount Mary University

Approved by:

Megan Baumler, PhD, RD, CD
Professor, Graduate Program in Dietetics

Tara LaRowe, PhD, RD, CD
Adjunct Professor, Graduate Program in Dietetics

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Abstract

Background: While research has helped to the support specific nutrition recommendations to aid in the prevention of cancer and the prevention of malnutrition during cancer treatment, where there still exists a gap in the literature is the role of specific diet interventions to increase sensitivity to conventional treatment. The Ketogenic diet has been proposed as a way to favorably alter metabolism to prevent the growth of malignant disease.

Objective: This project is a research proposal for a study to assess if the Ketogenic diet affects response to first line therapy in individuals diagnosed with stage IV colon cancer compared to individuals who follow a standard Western diet.

Methods: Following enrollment individuals will be randomized to an intervention or control group. Those in the intervention group will be instructed to follow a Ketogenic diet, with a 3:1 fat to protein and carbohydrate ratio for 12 weeks. All participants will be prescribed first line chemotherapy by a medical oncologist. Disease status will be assessed at the beginning and end of the intervention through fluorodeoxyglucose positron emission tomography (FDG-PET).

Anticipated Results: Based on past pilot studies, it is anticipated more participants in the intervention group who achieve a stable level of ketosis will have progression free survival or disease regression. Those following the Ketogenic diet will have increased quality of life, improvements in low density lipoprotein (LDL) and hemoglobin A1c, and insignificant lean body mass preserving weight loss.

Concerns: Potential complications included low enrollment, lack of compliance the intervention, and delay of chemotherapy.

Application: Further literature assessing the impact of a specific diet on disease status during treatment can provide evidence based recommendations to help empower patients to play a role in their own care. The Ketogenic diet may also be a means to increase sensitivity to conventional therapy, increasing survival rates.

Future Research: Following the completion of this pilot study, future research will be needed to identify length of time participants needs to remain compliant to the Ketogenic diet, appropriate macronutrient breakdown, safety in high nutritional risk populations, and determination of who will benefit from the intervention.

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Chapter 1: Introduction

Behind cardiovascular disease, cancer is the second leading cause of death within the United States (Centers for Disease Control and Prevention, 2016). Cancer is broadly defined as the uncontrolled growth and division of abnormal cells. Cancer cells are considered abnormal due to their malignant nature, lack of specialization, resistance to apoptosis, stimulation of angiogenesis for tumor growth, and evasion of the immune system (National Cancer Institute, 2015). According to the National Cancer Institute, two fifths of men and women will be diagnosed with cancer at some point in their lifetime (2017). The top four cancers diagnosed within the United States include breast, prostate, lung, and colorectal. Women have a one in eight chance of being diagnosed with breast cancer while men have a one in nine chance of being diagnosed with prostate (American Cancer Society, 2018). The cost of care for this chronic disease using conventional medicine is estimated to grow to $156 billion by the year 2020 (National Cancer Institute, 2017).

Due to advancements in modern medicine, such as new radiation techniques and immunotherapy options, cancer related deaths decreased by 13% from 2004 to 2013 (National Cancer Institute, 2017). The five-year survival rates for late stage diseases however remains low. Low response rates combined with both short-term and long-term side effects makes non-pharmaceutical approaches to the management of cancer appealing to many individuals.

The Ketogenic Diet is a non-pharmaceutical approach to the management of cancer that is supported by a growing amount of cell and animal studies. The Ketogenic Diet was first developed by R.M. Wilder in 1921 for the treatment of pediatric epilepsy (Allen et al., 2014).

Wilder defined this diet, what is known now as the classical ketogenic diet, as a high fat low carbohydrate and low protein diet, meant to mimic a fasting metabolic state. The classical ketogenic diet is 90% fat, 8% protein, and 2% carbohydrate. This translates to a diet of a 4:1 ratio: four grams of fat to combined one gram of carbohydrate and protein. Common sources of fat include butter, heavy cream, various oils, nuts, and avocado. Individuals following this diet are encouraged to eat foods high in saturated fat unlike dietary recommendations aimed at the general public. After a few days of following this altered eating pattern, cells in the body are forced to oxidize fatty acids to produce ketone bodies to be used as a primary energy source, rather than glucose. Compliance to the ketogenic diet can be assessed with urinary or serum measurement of the primary ketone body, beta-hydroxybutyrate. Reliance on ketones bodies for energy is an efficient way to maintain energy levels due to the effect of ketones on metabolism: ketone bodies increase the free energy generated during adenosine triphosphate hydrolysis (Paoli, Rubini, Volek & Grimaldi, 2013).

Multiple theories, documented in animal and cell models, support the use of the ketogenic diet for disease control in oncology patients. These theories include the Warburg Effect, upregulation of the mammalian target of rapamycin (mTOR) pathway, and the role of insulin like growth factor-1 (IGF-1) on cell growth. The Warburg Effect and the changes in mTOR pathway signaling are thought to be due to innate mitochondrial dysfunction of malignant cells (Paol et al., 2013). Excessive levels of circulating IGF-1 are due to a high intake of carbohydrates. Reducing carbohydrate intake, therefore, may reduce the activity of this growth hormone.

As cancer continues to outsmart modern medicine, as evidenced by low survival rates in specific patient populations, looking at non-pharmaceutical ways to lengthen progression free survival and/or increase sensitivity to conventional treatment are needed. Based on animal and cell studies, the ketogenic diet seems like a reasonable way to manipulate metabolism to improve patient outcomes. Some human studies have used a modified ketogenic diet, while others have used a low carbohydrate diet with higher intakes of both protein and fat. One of the most commonly referenced articles on the topic was published by Zuccoli et al. (2010), and showed the benefit of a calorie restricted ketogenic diet in a patient with glioblastoma multiforme. However, intervention studies are limited to those evaluating safety and feasibility, and furthermore, have been focused on the use of a carbohydrate restricted or ketogenic diet in individuals whose disease has not responded to convention al therapy alone. These include studies published by Schmidt, Pfetzer, Schwab, Strauss & Kammerer (2011), Tan-Shalaby et al (2016), Rieger et. al (2014) and Fine et al. (2012). A study conducted by Klement and Sweeney (2016) assessed how the ketogenic diet affected body composition during conventional therapy to determine if undesired muscle wasting would occur.

Based on the available research, the ketogenic diet is safe and arguably feasible in late stage cancer patients; thus, it is logical to begin studying the effect of this intervention on disease progression when combined with conventional therapy. The purpose of this study proposal will be to examine the effect of a ketogenic diet combined with first line conventional therapy on disease status in individuals with stage IV colon cancer, compared to a control group also on conventional therapy and a standard Western diet. A validated questionnaire will be used to assess quality of life, biomarkers to assess metabolic changes, anthropometric changes

during the study, and disease status will be assessed using fluorodeoxyglucose positron emission tomography (FDG-PET) imaging. Additionally, biopsies of malignant tissue will be taken to determine if ketolytic enzymes are present or absent. While many of the studies referenced above included individuals with varying primary solid tumors, an intervention group with close to normal metabolic needs would be ideal to decrease the risk of intervention related malnutrition. Of the most commonly diagnosed cancers with low survival, colorectal cancer patients have been shown to have metabolic rates similar to those without a cancer diagnosis (Ceolin Alves, Zuconi, & Correia, 2016).

The results of this study could be impactful for patients because the ketogenic diet could help to extend life. A positive response to the diet could transition patients from stage four to state three or two and make them eligible for interventions that are usually for curative intent, such as surgery. Additionally, one of the most appealing aspects of this type of intervention from a patient's stand point is that it is something they can control. With the ketogenic diet patients can feel confident they are playing a role in the outcome of their disease that often feels out of one's control. For clinicians, more research to provide evidence-based recommendations during treatment in the oncology population would be helpful since research regarding diet recommendations during treatment are overall limited.

Research Question

1. How does the Ketogenic diet affect response to treatment in individuals diagnosed with stage IV colon cancer on first line therapy, compared to individuals who follow the standard Western diet while on first line therapy?

Subproblems

1. How does the Ketogenic diet impact quality of life in late stage cancer patients?
2. Does the intervention cause significant changes to biomarkers such as a lipid panel and hemoglobin A1c?
3. Does the level of ketosis impact response to treatment?
4. How does the presence of ketolytic enzymes affect response to intervention?
5. What is the effect of a eucaloric ketogenic diet on body composition?

Limitations

1. Number of individuals eligible for study enrollment based on inclusion criteria
2. Accuracy of self-reported data throughout the study period

Delimitations

1. This study will only include well nourished individuals based on SGA criteria
2. Individuals on insulin or those with a history of hyperlipidemia will not be eligible for enrollment

Assumptions

1. Individuals who are enrolled in the study are motivated to complete the study due to the restrictive nature of the intervention
2. The intervention will not provide harm to patients
3. Results of this study will be meaningful to the field of dietetics

Definition of Terms

Albumin – a serum protein produced by the liver largely responsible for maintaining fluid balance.

Bioelectric impedance analysis (BIA) – method of assessing body composition, body fat, fluid status, and lean body mass. Measured with a low amount of electrical current. Differing tissues provide different amounts of resistance.

Cachexia – the progressive loss of subcutaneous fat and lean body mass that eventually leads to impaired ability to complete activities of daily living and poor tolerance to cancer treatment.

Carbohydrate – typically, the major source of energy in the diet. Molecule manufactured by plants composed of carbon, hydrogen, and oxygen. Dietary carbohydrates can be categorized as monosaccharides, disaccharides, polysaccharides, and oligosaccharides. Examples of carbohydrates in the diet include fruit, fiber present in vegetables, grains, most legumes, dairy products, juices, and baked goods (Mahan, Escott-Stump & Raymond, 2012).

Cells – the smallest structural unit within the human body. The human body is composed of trillions of cells responsible for structure, nutrition, and energy as a few examples. Cells also hold genetic materials (Genetics Home Reference, 2018).

Computed tomography (CT) scan – a test used to create cross sectional images of various areas of the body. Similar to an x-ray, except three dimensional images are created to view areas of the body in significant detail (Radiological Society of North America, 2016).

C-reactive protein – a blood test used to assess/measure the amount of inflammation present in the body. Produced by the liver.

Cytosol – jelly like fluid within the cytoplasm (Genetics Home Reference, 2018).

Deoxyribonucleic acid (DNA) – genetic material of all living organisms. Changes or mutations within this genetic material can lead to cell growth or damage (Mahan, Escott-Stump & Raymond, 2012).

Eastern Cooperative Oncology Group (ECOG) performance status – method used to assess functional status of a patient. Scores range from 0-5. A score of 0 indicates a patient is fully active and able to function without restriction. A score of indicates a patient is dead (ECOG-ARIN Cancer Group, 2017).

Enteral nutrition – also commonly referred to as tube feeding. A source of alternative nutrition for individuals who are unable to meet their nutritional needs orally. Enteral nutrition can be provided to an individual through the stomach or small intestine.

Fluorodeoxyglucose position emission tomography (FDG-PET) scan – imaging technique that products a three dimensional image to evaluate functional processes in the body such as tumors, blood flow, and brain disorders. Prior to completion of the scan, a tracer fluorodeoxyglucose, is injected. This tracer will be absorbed rapidly by tissues with increased metabolism (American College of Radiology Imaging Network, 2018).

Gastrointestinal distress – in this instance, referring to physical gastrointestinal symptoms that can arise from medications or diet preferences. Gastrointestinal symptoms can include but are not limited to pain, gas, bloating, diarrhea, constipation, mucositis, or esophagitis.

Glycolysis – the metabolic process to break down glucose, carbohydrate, to form pyruvate and adenosine triphosphate to be used for cellular energy.

Hemoglobin A1c – blood test that provides an individual's average blood sugar over the past three months. The test assesses the attachment of glucose to hemoglobin, the protein in red blood cells. Red blood cells live an average of three months in the body. Normal values are less than 5.7% (National Institute of Diabetes and Digestive and Kidney Diseases, 2018).

Hyperuricemia – abnormally high levels of uric acid accumulation in the blood. This can occur while in a state of ketosis due to competition for renal secretion of organic acids and urate (Singh, Gomez, & Swamy, 2010).

Hypoglycemia – a state of low blood glucose often due to an inadequate amount of carbohydrate being present in the body. Signs and symptoms of hypoglycemia include dizziness, sweatiness, confusion, loss of consciousness and even death.

Indirect calorimetry – commonly used method to assess energy expenditure. Over a given period of time an individuals oxygen consumption and carbon dioxide production are quantified (Mahan, Escott-Stump & Raymond, 2012).

Insulin – a hormone made by the beta cells in the pancreas who's primary function is to allow cells to absorb glucose and use glucose for energy (National Institute of Diabetes and Digestive and Kidney Diseases, 2009).

Karnofsky Performance Score (KPS) – method used to assess functional status of a patient. Scores range from 0-100. A score of 0 indicates a patient is dead. A score of 100 indicates a patient is fully active and able to function without restriction (ECOG-ARIN Cancer Research Group, 2017).

Ketonuria – the presence of ketone bodies in the urine.

Ketosis – metabolic state characterized by elevated levels of ketones in body from fatty acid oxidation. This state is induced when levels of carbohydrates in the body become insufficient. Uncontrolled ketosis, present during diabetic ketoacidosis can be life threatening.

Leukocyte – also referred to as white blood cells, a type of blood cell made in the bone marrow as part of the body's immune system. Primary role is to fight infection and disease (National Cancer Institute, n.d.).

Lipid panel – a blood test to assess the amount of lipids present in the blood. Lipids assessed include low density lipoprotein, high density lipoprotein, and triglycerides.

Lymph node – a small structure that is part of the immune system responsible for filtering lymphatic fluid and storing white blood cells, lymphocytes. Spread throughout the body. Clusters of nodes are found in the neck, axilla, chest, abdomen, and grain (National Cancer Institute, n.d.).

Magnetic resonance imaging (MRI) scan – a scan completed to produce detailed images of internal structures using a magnetic field. This type of scan does not utilize x-rays.

Malnutrition – any nutrition imbalance. In the oncology setting, malnutrition is often referring to undernutrition, the lack of adequate calories, protein, and/or other nutrients needed for tissue maintenance and repair. Malnutrition can develop from inadequate intake, increased nutritional needs, malabsorption, and/or altered transport of nutrients (White et. al, 2012).

Mammalian target of rapamycin (mTOR) pathway – the key metabolic pathway controlling cell growth and proliferation. This pathway responds to stress, oxygen, energy, and growth factors. Mutations within this pathway are associated with growth of malignant cells (Addgene, n.d.).

Metastasis – the spread of cancer cells to another part of the body away from the primary tumor. Metastasis develop when malignant cells travel through the blood or lymph systemic (National Cancer Institute, n.d.)

Mitochondria – organelles within the cytoplasm responsible for converting energy from food into a useable form for cells (Genetics Home Reference, 2018).

Monotherapy – the use of only one therapy to treat or control a disease.

Mucositis – inflammation of the digestive system as a complication of cancer therapies, often present in the mouth.

Oxidation – metabolic process where oxygen is added to a compound. Referring to fatty acid beta oxidation. The metabolic process where fatty acids are broken within the mitochondria. In the mitochondrial matrix, long chain acetyl co-A is oxidized to acetyl coA. Acetyl coA then is converted to NADH and FADH2 using oxidation within the tricarboxylic acid cycle. The final byproduct of this pathway, adenosine triphosphate, is generated from the electron transport chain (Filmore, ALrob & Lopaschuk, n.d.).

Palliation/Palliative care – approach that improves the quality of life of patients and their families facing the problem associated with life threatening illness. Prevention and relief of

suffering are main focuses. This care is not for cure of disease (World Health Organization, 2018).

Parenteral nutrition – a source of alternative nutrition for individuals who are unable to meet their nutrition needs orally. This method of feeding is indicated in individuals who have a non-functioning gastrointestinal tract or who have failed to tolerate enteral nutrition. Parenteral nutrition is administered intravenously.

Resting energy expenditure – the amount of energy expended while at rest.

Satiety – the feeling of fullness following energy intake

Sensitivity – how well the body responds to a particular treatment. Related to cancer, an individual is more sensitive to a treatment their cancer would respond in a positive way.

Chapter 2: Literature Review

Introduction

In 1975, the top five leading causes of death within the United States according to the Centers for Disease Control and Prevention (CDC) were heart disease, cancer, stroke, accidental injuries, and influenza. Despite significant advances in medicine, the top two leading causes of death have remained unchanged over 40 years later. Based on the latest CDC data from 2015, heart disease and cancer continue to be the leading causes of death within the United States. Each condition accounts for 23.4% and 22.0% of death respectively (CDC, 2016). While heart disease is the number one leading cause of death, a new diagnosis of hypertension does not often cause the same level of concern a cancer diagnosis does. Perhaps an individual is more concerned with a cancer diagnosis because it is a disease that continues to circumvent researchers and health care professionals alike.

A simple definition of cancer is the uncontrolled growth and division of abnormal cells. The human body consists of 30 to 40 trillion cells meaning there is an abundance of opportunities for abnormal cell growth to go unnoticed (National Cancer Institute, 2015). Normal human cells grow and divide based on need. As a normal cell becomes old or damaged, it dies, allowing a new healthy cell to take it's place. Cancer cells on the other hand, become damaged, but are able to survive due to a number of mechanisms. These mechanisms include their malignant nature, meaning ability to grow or invade surrounding tissues, lack of specialization, resistance to apoptosis or cell death, stimulation of new blood vessels, angiogenesis, for tumor growth, and evasion of the immune system. When cancer cell growth continues uninterrupted, a collection of abnormal cells develops. This is most often referred to

as a solid tumor. Solid tumors are not characteristic of cancers of the blood such as leukemia, lymphoma, and myeloma. Malignant tumors differ from benign tumors. Benign tumors are non-life threatening unless found in the brain.

According to the National Cancer Institute (2017), 40% of men and women will be diagnosed with cancer during their lifetimes. The top four cancers diagnosed within the United States include breast, prostate, lung, and colorectal. Women have a one in eight chance of being diagnosed with breast cancer while men have a one in nine chance of being diagnosed with prostate (American Cancer Society, 2018). From 2004 to 2013, cancer related deaths have decreased by 13% (National Cancer Institute, 2017). While this statistic is encouraging, survival rates for individuals diagnosed with late stage disease remain low. Despite advances in modern medicine such as new radiation techniques and more targeted intravenous options, the five-year survival rate for individuals with stage IV disease vary from 29% for prostate cancer, 11% for colon cancer, and less than 10% for lung, pancreatic, and liver (American Cancer Society, 2017).

Within the next decade, the chance of receiving a cancer diagnosis is anticipated to increase. According to the National from 2012 to 2030 the number of worldwide cancer diagnoses will increase from 14 Cancer Institute, million to 21 million. With an increase in diagnoses, there will also be an increase in the cost of care. In 2015, the cost of caring for individuals with a cancer diagnosis was $80.2 billion. More than half of this cost was generated from outpatient office visits. Around 38% of this cost was due to inpatient admissions (American Cancer Society, 2018). The cost of care for this chronic disease using conventional

medicine is estimated to grow to $156 billion by the year 2020 (National Cancer Institute, 2017).

Much of the cost of cancer stems from treatment of the disease, whether for curative intent or disease management. Conventional treatment options for cancer include chemotherapy, radiation therapy, and surgical intervention for cure or palliation. Chemotherapy, sometimes referred to as cytostatic or systemic therapy, affects more areas of the body than radiation therapy or surgical intervention. All conventional treatments have side effects for patients. Side effects of treatment can vary from gastrointestinal distress to burns to delayed wound healing and scarring. The use of complementary medicine is often used with conventional therapy to decrease side effects and/or increase efficacy of treatment. Complementary medicine includes but is not limited to the use of herbs and supplements, acupuncture, and nutritional intervention. For example, supplementation with omega-3 fatty acids in individuals with cancer cachexia has been shown to preserve lean body mass (Pappalardo, Almeida, & Ravasco, 2015). Curcumin supplementation has been studied in a variety of cancer types included colorectal, pancreatic, and breast, for it's role in decreasing inflammation and increasing sensitivity to conventional therapy (Gupta, Patchva, & Aggarwal, 2013).

Nutritional management of cancer patients often depends on the stage of the disease. During treatment, nutritional interventions are focused on managing side effects, maintaining lean body mass, and preventing weight loss. After treatment, nutrition intervention is focused on preventing recurrence of disease.

Interest is continuing to grow in the role nutrition can play related to cancer management. There are a number of eating patterns promoted for individuals with cancer, many of which are overly restrictive, difficult to comply to and unsupported by research. Examples of these nutrition protocols include the highly criticized Gerson Diet, in which an individual consumes homemade juice hourly, and the Alkaline Diet which claims to change the pH of the blood, thus preventing cancer growth. More recently, the Ketogenic Diet (KD) is another therapeutic diet promoted for cancer patients. The KD is both restrictive and difficult to comply with, but this diet differs in that research has been conducted and more is underway to determine if it may be an effective intervention for cancer management.

The KD was developed in the early twentieth century as a treatment option for pediatric epilepsy. The intent of the diet is to mimic a state of fasting with a high fat and a very low carbohydrate intake. With carbohydrate restriction, circulating insulin levels decrease forcing the body's primary fuel source to switch ketones, a metabolic byproduct of fatty acid oxidation (Paoli et al., 2013). Since it's development, research for the use of the KD has grown to include weight management, diabetes mellitus, heart disease and now cancer. There are also a number of cell and animal studies published that demonstrates it's efficacy in aiding in disease management of malignancy. The purpose of this literature review is to critically analyze the evidence on the Ketogenic Diet in various solid tumor types in humans. This review will provide further background on the studied uses of the diet, macronutrient composition, possible negative side effects of the diet, proposed mechanisms of action, and cancer staging and treatment. A review of the currently available literature can help healthcare professionals

provide oncology patients with more specific nutrition recommendations in an effort to improve their health outcomes.

Background

Cancer staging and treatment.

At the most basic level, cancer is a genetic disease. Genetic changes to cells can be inherited maternally or paternally however only 5-10% of cancers are attributed to these genetic defects. The remaining 90-95% of genetic changes that lead to cancer cell growth are thought to be caused by lifestyle factors including cigarette smoking, alcohol consumption, diet, stress, obesity, physical inactivity, sun exposure, and environmental exposures. Many of these lifestyle factors are considered modifiable (Anand et al., 2008). Genetic changes in malignant cells are most commonly seen in three different groups of genes. The term oncogene refers to an altered gene that allows cells to survive and often grow uncontrollably. Mutations in tumor suppressor genes also contribute to excessive cell growth. When there are mutations present in these genes, tumor suppressor proteins are incorrectly produced leading undesired cell growth. Deoxyribonucleic acid (DNA) repair genes are the last common group of genes where mutations are commonly seen. If DNA repair genes are unable to repairs genetic mutations, these mutations can eventually become cancerous (National Cancer Institute, 2017).

The various treatment options that currently exist for cancer are developed to target the genetic defects present in malignant cells. Conventional treatment options for cancer include chemotherapy, radiation therapy, and surgical intervention. The type of treatment offered to a patient often depends on the stage of the disease. The most common tool used by medical professionals for the staging of cancer is the Tumor Node Metastasis (TNM) staging

system. This system was developed jointly by the American Joint Committee for Cancer and the Union for International Cancer Control. The primary tumor found in an individual can be classified from T0 to T4. T0 indicates there is no evidence of a primary tumor. T4 tumors are large masses that likely have grown into nearby tissues. The N value in this system refers to nodes, lymph nodes. If an individual is staged N0 this indicates there is no cancer found in the lymph nodes. N1-N3 values indicate there is regional lymph node involvement, N3 being the most widespread. Metastasis are simply classified as M0 or M1 indicating if distant metastasis are or are not present. Often times to simplify staging, the TNM scores are combined into an overall score, the commonly referred to stage I, II, III, or IV diagnosis (American Joint Committee on Cancer, 2018).

All of the therapy options for cure or control can have significant side effects for patients. Chemotherapy is defined by the American Cancer Society as the use of a drug to treat a disease (American Cancer Society, 2016). Chemotherapy, also referred to as cytostatic drugs, can be used in every stage of cancer, however it is most often the primary treatment modality in individuals with metastatic disease because it is a systemic therapy that targets various areas of the cell cycle to stop cell division and replication. Unlike radiation and surgery, chemotherapy can be utilized by tissues throughout the body with the intent of controlling disease in more than one location. Side effects of cytostatic therapy are most prevalent in non-cancerous cells that multiply quickly such as blood cells, hair follicles, and mucous membranes throughout the mouth and gastrointestinal tract. These side effects interfere with eating and may present as nausea, vomiting, diarrhea, constipation, mucositis, or taste changes (“How Does Chemotherapy Work?”, 2016). Like chemotherapy, radiation therapy can also cause

damage to non-malignant cells when used as treatment. Radiation therapy works to destroy cells by causing DNA damage. As radiation is administered ionization occurs within DNA strands leading to broken bonds. Malignant cells are less able to repair this damage compared to normal cells. Normal cells however can still experience short or long-term damage. Radiation is unlike chemotherapy, in that it is a much more precise treatment usually targeting a specific area where cancer is present (Mitin, 2017). Depending where radiation is administered, again a patient's ability to eat can be impaired in addition to significant fatigue, discomfort at treatment site and even external burns. Surgery, the physical removal of the cancer, is another conventional treatment option. Surgery can be for both curative and palliative intent depending on the state of the disease. Tumors can be fully excised from the body or partially removed which is commonly referred to as debulking. Some tumors cannot be fully removed because the damage would be too significant. Chemotherapy, radiation therapy, and surgery can all have long term effects for patients.

The National Comprehensive Cancer Network (NCCN), is a non-profit organization devoted to development of education, research, and patient care (National Comprehensive Care Network, 2018). The organization was initially established in 1995 and has since become an alliance of 27 leading cancer centers that provides the framework of care for physicians to utilize when making treatment plans for patients. NCCN guidelines are often utilized to justify treatment decisions when seeking insurance coverage for patients. Guidelines are published for each primary tumor site as new research becomes available. The most recent NCCN guidelines for the treatment of colon cancer were published in 2018. These guidelines cover patient care

protocols regarding imaging from initial workup to surveillance, pathologic review, surgical intervention, radiological intervention, systemic therapy, and survivorship.

Nutritional management of adult oncology patients.

Current evidence-based nutrition recommendations for the adult oncology patient during treatment are the same regardless of the intent of treatment. With the multitude of side effects that can occur during cancer treatment and the unique metabolic needs of cancer patients, it is the role of a nutritional professional to help manage these barriers to reduce the risk of malnutrition. Malnutrition has been reported in anywhere from 30% to 85% of cancer patients (Arends et al., 2016). Poor nutritional status is a concern for patients undergoing treatment because it has been well established malnourished individuals have poorer outcomes, poorer tolerance to treatment, and are at a higher risk of inpatient admissions. All of these outcomes can be associated with increased healthcare costs. It is thought malnutrition rates are often under reported because it is difficult to define malnutrition. In many institutions a screening tool is used to assess nutritional status. A common tool in the oncology setting is the Patient Generated Subjective Global Assessment (PG-SGA). This tool has been validated in both inpatient and outpatient setting. Depending weight change, gastrointestinal issues and daily activities patients are classified as well nourished, moderately malnourished, or severely malnourished (PDQ Supportive and Palliative Care Editorial Board, 2017). Screening tools for malnutrition are important to utilize because accurate biomarkers for nutritional status still have not been developed. Although C-reactive protein and albumin can help to assess the extent of systemic inflammation, both markers are produced by the liver and can therefore be impacted by abnormal liver function (Arends et al., 2016).

The metabolism of cancer patients is altered from that of individuals without a malignant diagnosis. A recently published article by the European Society of Parenteral and Enteral Nutrition outlines the catabolic alterations that occur in cancer patients (Arends et al., 2016). Catabolism is the breakdown of molecules. Inadequate nutritional intake can occur in this population due to naturally occurring mechanisms, anorexia and cachexia, but can be worsened by secondary causes such as side effects of treatment and bowel failure or obstruction. The catabolism that has been illustrated in a number of studies evaluating cancer patients is the breakdown of lean body mass. Researchers have seen the loss of skeletal muscle mass often times without the loss of fat, which is one of the main aspects associated with malnutrition. The progressive loss of muscle mass is what contributes most significantly to impairment, surgical complications, toxicity of chemotherapy and mortality. With the rapid protein catabolism that can occur in patients, nutritional management should be focused on maintenance or gain of muscle

Systemic inflammation syndrome is another way the metabolism of cancer patients is altered. This metabolic state can alter metabolism of all three macronutrients, carbohydrate, fat, and protein. Carbohydrate metabolism in the presence of systemic inflammation presents as insulin resistance and impaired glucose tolerance. Oxidation of lipids is increased contributing further to involuntary weight loss. Protein metabolism changes were described above.

Various ways to assess lean body mass wasting have been developed so that is can be identified and addressed as needed. These methods vary from the use of skin calipers,

completing the Nutrition Focused Physical Assessment, bioelectric impedance analysis, and a newer more precise method of evaluating sarcopenia on computed tomography (CT) scans.

Following assessment and diagnosis of malnutrition, nutrition intervention commonly begins with recommendations for calorie and protein needs. Recommendations for the most appropriate oral nutrition supplements and diet recommendations for symptom management are also usually part of the nutrition intervention. Energy requirements of cancer patients can vary. Patients with some primary cancer types, such as pancreatic and lung, have been noted to have higher resting energy expenditures (REE), while patients with other cancer types such as colon, have been noted to have metabolic rates similar to controls. A 2011 study by Gonzalez Vela et al., assessed the REE of 20 individuals with metastatic colorectal cancer. Only individuals with liver metastases had a statistically significant increased REE compared to controls. Lieffers et al. (2009) concluded similar data for individuals with metastatic colorectal cancer but noted metabolic rates were linearly related to increases in mass of highly metabolic tissues such as the liver. The gold standard for assessing REE is indirect calorimetry however, this method of assessment however is costly and time intensive. The predictive equation, 25-30 calories/kilogram can be used instead, and adjustments can be made to calorie recommendations based on weight change (Arends et. al, 2016).

Recommended protein intake should be between 1 gram/ kilogram of body weight/day to 1.5 grams/kilogram of body weight/day. Research still needs to be conducted to evaluate which types of amino acids are most beneficial. If energy and protein needs cannot be meet orally during treatment, artificial nutrition can be started and monitored by the RD. This can take the form of enteral or parenteral nutrition. Drug therapy can also be helpful in managing

malnutrition. Medications exist for appetite stimulation, increased gut motility, improvement of anabolism, and decrease in systemic inflammation. Nutrition professionals can work with oncologists to make appropriate recommendations for these medications. Nutrition counseling from a registered dietitian (RD) is imperative during treatment to help guide patients in how to meet protein and energy needs, manage side effects or treatment, and use their nutrition to help maintain quality of life.

For patients that are receiving treatment for curative intent of disease, it is also the role of the nutrition professional to provide recommendations to reduce the risk of recurrence or another primary malignancy. The American Institute for Cancer Research (AICR) provides detailed diet and lifestyle recommendations for reducing an individual's risk of malignancy. The AICR is an independent organization established almost 40 years ago with the sole intent of looking at the connection between diet and cancer through analysis of completed research studies and completion of new research studies. From the available literature, the institute has developed the following recommendations for individuals (2018).

- Maintain a healthy body weight without being underweight.
- Include physical activity every day with a goal of 30 minutes daily
- Limit/avoid sugary beverages and energy dense foods such as fast food
- Eat a plant-based diet high in fruits, vegetables, whole grains, beans, nuts, and seeds
- Limit consumption of red meats to 18 ounces/week.
- Avoid processed meats as often as possible
- Alcohol consumption should be limited to 2 servings daily for men and 1 serving daily for women

- Limit sodium in the diet to less than 2400 milligrams daily
- Abstain from tobacco use
- Focus on diet and lifestyle, not supplements for protection again cancer

Other organizations have also published guidelines for cancer survivors, such as the World Cancer Research Fund. The common trend among each set of recommendations is to maintain a healthful body weight with a plant-based diet and regular physical activity.

The ketogenic diet.

While there is a significant amount of literature available regarding how to prevent malnutrition during cancer treatment and how to prevent recurrence of disease, there is an area of oncology where nutrition research is still lacking. This gray area of oncology related nutrition is the role nutrition plays in regards to sensitivity to conventional therapies such as chemotherapy and radiation. Based on animal and cellular studies, the Ketogenic diet (KD) is quickly gaining interest for its use in oncology patients. While the KD was originally developed by Dr. Wilder at the Mayo Clinic in the 1920's for the treatment of pediatric epilepsy, a modified version of the diet made waves again in the late twentieth century for weight loss (Zupec-Kania, Abrahams, & Pietsch-Escuda, 2016).

Unlike the popular Atkins Diet which is simply low in carbohydrates, a conventional KD is a high fat and very low carbohydrate diet meant to induce a metabolic state similar to that of fasting. Macronutrient breakdown of the conventional Ketogenic diet is a 4:1 or 3:1 ratio of grams of fat to combined grams of carbohydrate and protein. This translates to a diet that provides 90% of calories from fat, 8% from protein, and 2% from carbohydrate (Allen et al., 2014). To meet fat needs for a day, both saturated and unsaturated fats are consumed. The KD

is also sometimes referred to as very low carbohydrate ketogenic diets (VLCKD). After three to four days of very low carbohydrate intake glucose stores are depleted, forcing the metabolic shift to fatty acid oxidation for the primary energy source. The body's fuel source transitions to fatty acids because the central nervous system, which preferentially utilizes glucose, is also capable of using specific ketone bodies, byproducts of fatty acid metabolism, for energy (Paoli, Rubin, Volek, & Grimaldi, 2013). Fatty acids are converted into ketone bodies in liver mitochondria through beta-oxidation, the catabolic formation of energy. Increased fatty acid beta-oxidation then leads to increased production of acetyl-CoA. Under normal metabolic conditions, acetyl-CoA is produced when pyruvate from glycolysis is oxidized. In both metabolic situations, acetyl-CoA then enters the tricarboxylic acid cycle for complete oxidation. Under conditions with a lack of carbohydrate is present, the amount of acetyl-CoA produced exceeds the capacity of the tricarboxylic acid cycle, leading to the production of ketone bodies, which are incompletely oxidized fatty acids. The primary ketone bodies produced by the liver mitochondria that can be used for energy throughout the body including the central nervous system are, include beta-hydroxybutyrate (BHB) and acetoacetate (Woolf & Scheck, 2015). Ketone bodies produce more energy compared to glucose. An important differentiation between metabolic ketosis and diabetic ketoacidosis is the level of serum ketones. Serum ketone body concentrations on a KD may be up to 7-8 mmol/L, while on a standard diet of 40-60% carbohydrate concentrations may be less than 0.3 mmol/L. During diabetic ketoacidosis, serum ketone body concentrations increase to greater than 25 mmol/L leading to a potentially fatal change in serum pH (Paoli et al., 2013).

When individuals follow a KD it is often advised they self-assess urinary ketones using over the counter reagent strips during a specific period of time to ensure the desired metabolic shift has occurred. A recent study published by Urbain and Bentz (2016) determined that the most reliable time of day to assess urinary ketones is in the early morning or post-prandially in the evening. This study was a substudy of another completed by the same researchers. Twelve subjects from the other study, without a cancer diagnosis, assessed their urinary ketones at various times of day during the sixth week of the study. Urinary ketones were measured eight times a day during this period. Results of these measurements showed the highest detection rates, above 90%, were seen at 7 am, 10 pm, and 3 am. Although this study evaluated a small sample size, it provides some guidance for further studies on when urinary ketones should be assessed.

The KD has been researched in a variety of populations. According to Zupec-Kania et al. (2016) epilepsy is the only disease state randomized control trials exist on to support the use of this nutrition intervention. For more common diseases such as diabetes, obesity, cardiovascular disease (CVD), and cancer, the research is still developing. Most of the studies in these populations have been conducted without control groups or as case studies. A different article by Paoli et al. (2013) argues there is strong evidence for the use of the KD in obesity, diabetes mellitus, and CVD. In regards to obesity, there are a few proposed mechanisms of action regarding why the diet is effective. Studies have concluded the KD increases satiety, causes changes in both ghrelin and leptin, directly suppresses appetite due to ketone bodies being present, reduces lipolysis, and increases metabolic rate all to promote weight loss. With CVD, research has shown the diet to have a positive effect on lipid profiles which seems

counterintuitive due to the fat content of the diet. The nature of the diet, very low carbohydrate, has been seen to also benefit those with diabetes mellitus. Insulin resistance is the primary reason impaired fasting glucose occurs in individuals with type II diabetes mellitus. With insulin resistance, a larger amount of dietary carbohydrates is metabolized into fat in the liver rather than being used for energy in skeletal muscle. With a carbohydrate restriction in place there is not enough carbohydrate rich energy being consumed to be converted to fat, positively impacting insulin resistance. The research for the use of the KD in the oncology population is still developing. The published research for cancer will be discussed in much greater detail later in this paper.

Adverse effects.

Manipulating the body's primary fuel source does not come without possible acute and chronic side effects. A review article by Allen et al. (2014) outlined common side effects seen in with a KD. Side effects have been most often evaluated in pediatric and adolescents study groups compared to adults. Acute side effects of the diet can include gastrointestinal distress, lethargy, hypoglycemia, and trace mineral deficiencies. Nausea and vomiting can occur with the delayed gastric emptying associated with a high fat intake. Constipation occurs due to very low fiber intake. Individuals following a KD consume low amounts of high fiber foods fruits, grains, beans, and even vegetables. Nuts, seeds, avocado and fiber supplements are the primary fiber sources individuals can consume. Often, fiber supplements are needed to reduce diet associated constipation. With severely limited carbohydrate intake it is reasonable that hypoglycemia is a concern. Patients following a KD should be educated on not only the signs and symptoms of hypoglycemia but also how to correct for the condition. In this specific

instance, increased carbohydrate intake is indicated. While there are no guidelines published for the monitoring of hypoglycemia, if an individual is symptomatic frequently, self glucose monitoring may be indicated. Trace mineral deficiencies of zinc, selenium, and copper have been seen in individuals following a KD. Based on the foods groups limited, whole grains and beans, there might also be concern for deficiencies of various B vitamins. While on the diet supplementation of trace minerals and B vitamins could help prevent deficiencies.

Chronic risks associated with a KD include increased low density lipoprotein (LDL) cholesterol, bone mineral loss, kidney stones, and renal damage. As stated above there is also evidence to show a KD can be beneficial for CVD. From the Allen et al. (2014) article changes in LDL levels in past studies were not reported to be significant. Studies evaluating changes to high density lipoprotein (HDL) were not discussed. Bone mineral losses, a reduction of calcium, phosphorus, or magnesium that can lead to weakening of bones, were again seen in the pediatric population. Bone mineral status could be assessed in adults with long term compliance to the diet with subsequent interventions implemented as needed. The risk of renal damage and kidney stones will on a KD is relatively low. This is a possible side effect due to calcium release, bone demineralization, that occurs with chronic metabolic acidosis. Chronic low urine pH additionally reduces solubility of uric acid increasing risk of stone formation.

Overall, the reported adverse effects of the KD in studied populations are low. Both acute and chronic side effects can be managed with supplements, medications, and if necessary brief alterations to diet composition.

Proposed mechanisms of action for cancer.

Previous research conducted on cancer cell metabolism has contributed to the growing interest of the use of KD in the oncology population. Based on established metabolic processes seen in malignant cells, a state of ketosis may aid in decreasing of activity of cancer cells. Around the same time the KD was first developed, the Warburg Effect was also proposed by Dr. Otto Warburg (Paoli et al. 2013). Warburg proposed due to mitochondrial dysfunction, cancer cells regardless of the presence or absence of oxygen will generate energy through a high rate of glycolysis in the cytoplasm. Lactic acid fermentation is increased with the process changing the pH of the cell. This method of energy production is inefficient because less molecules of adenosine triphosphate are produced as more glucose molecules are consumed. In normal cells, energy is only produced on this pathway in an anaerobic state. Additionally, in healthy cells glycolysis occurs in the cytoplasm whereas energy production from the citric acid cycle and electron transport chain occur in the mitochondria. With past research noting the absence of the citric acid cycle and electron transport chain in malignant cells, it is logical that mitochondrial dysfunction contributes to cancer cell metabolism. Because a higher amount of glucose is needed to support cancer cell metabolism, a diet low carbohydrates might induce death of cancer cells and decrease cancer cell proliferation.

Mitochondrial dysfunction of malignant cells is also thought to upregulate enzymes involved in the mammalian target of rapamycin (mTOR) pathway. Activation of this pathway increases resistance to apoptosis (Paoli et al, 2013). Both glucose and insulin are known to affect tyrosine kinase receptors that also activate this pathway. When this pathway is active, glucose uptake into cells is increased allowing for increased metabolic activity. Reduction in

glucose, may reduce the activation of this pathway that malignant cells are prone to (Strowd & Grossman, 2016).

Another theory that supports the benefit of the KD against malignant cells is the role of insulin like growth factor-1 in cell growth. Insulin like growth factor-1 is a growth hormone in the body responsible for cell proliferation. Because the purpose of this protein is to grow new cells, it contributes to resistance of apoptosis. As serum levels of insulin increase, largely based on carbohydrate consumption, hepatic production of insulin like growth factor-1 binding protein decreases therefore increasing levels of free circulating insulin like growth factor-1 (Paoli et al., 2013). Previous studies have shown individuals taking medications without an effect on insulin levels, such as Metformin, experience lower rates of malignancy compared to medications that impact insulin secretion (Rieger et al., 2014). Metformin belongs to the drug class biguanides. In the body biguanides assist in glycemic control by decreased hepatic glucose production. Other medications for glycemic control such as those in the sulfonylurea class, work to improve glycemic control by stimulating insulin release from pancreatic beta cells (Khardori, 2017). These medications in turn, increase IGF-1 production and possibly cell growth. Additionally, hyperglycemia in the oncology population has been linked to poor prognosis (Schwartz et al., 2015). Excessive carbohydrate intake is a contributing factor to hyperinsulinemia, higher than normal levels of insulin in the body, and therefore increased IGF-1 production.

Along with carbohydrate metabolism, it is also hypothesized some tumors may lack the necessary enzymes to use ketones bodies effectively. If malignant cells cannot use ketones bodies for energy in the absence of glucose, the cells will not be able to survive. Ketolytic

enzymes, which allow ketones to be used for energy in the human body, that have been assessed in studies include 3-oxoacid CoA transferase and beta-3-hydroxybutyrate dehydrogenase. Tumors with higher or lower amounts of these enzymes may respond differently to the diet an individual is consuming (Schwartz et al., 2015).

Body of Evidence

Primary brain tumors.

A case report published by Zuccoli et al. (2010) detailed the use and subsequent impact of a calorie restricted ketogenic diet (CRKD) on a patient with a newly diagnosed glioblastoma multiforme (GBM) undergoing conventional therapy. Throughout the case report, total time of ten months from diagnosis to time of recurrence of disease, the patient's weight, body mass index (BMI), urinary ketones, complete blood count, comprehensive metabolic panel, and disease status with magnetic resonance imaging (MRI). The patient was a 65 year old female who self-elected to follow a CRKD. At diagnosis, December 5th, weight was 141 pounds, BMI 25.6 kg/m^2. Prior to treatment, an MRI was completed. The patient was then started on steroids and anti-epileptic therapy. On December 15th a right frontal temporal craniotomy was performed. During the post-operative period, the patient self-elected to follow a two-day water fast followed by five days of very low oral intake and then another two day water fast. On December 24th, urinary ketones were present and average blood glucose decreased to 60 mg/dL from 130 mg/dL. Body weight had decreased to 127.6 pounds. At this time the patient began to follow a CRKD. Daily calorie intake was only 600 calories. Macronutrient composition was as follows 32 grams of protein (21%), 10 grams of carbohydrates (7%), and 42 grams of fat (63%). After 14 days of following the CRKD, the patient was started on concurrent

chemotherapy and radiation. Steroids were weaned. The patient's weight had decreased further to 121 pounds, a 14% weight loss over a one-month period. After completion of chemotherapy and radiation, an MRI scan on February 24th showed no evidence of a tumor or edema. Another MRI on July 22nd showed no evidence of disease. The patient had continued to follow a CRKD over this time facilitating further weight loss to 110 pounds, BMI of 20 kg/m^2. Following the third MRI, the patient chose to no longer monitor calorie intake. By October, disease recurrence was present. Figure 1 below illustrates a timeline for this case researchers included in the final report.

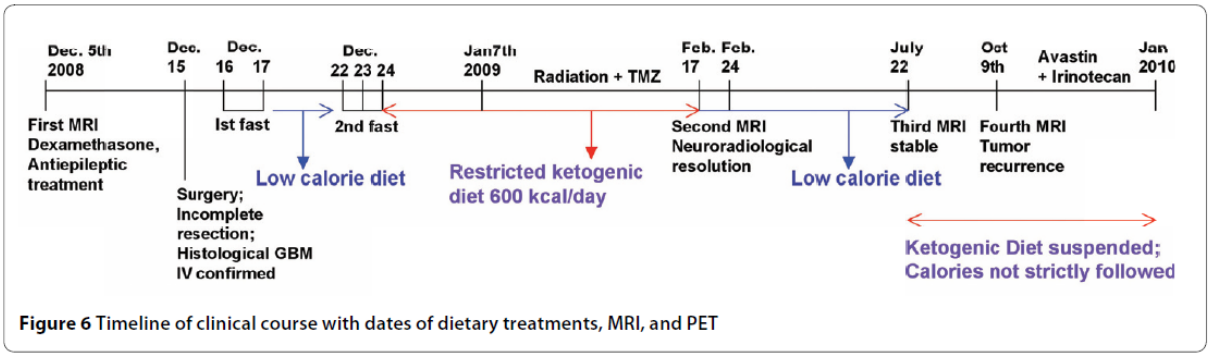


Figure 6 Timeline of clinical course with dates of dietary treatments, MRI, and PET

Figure 1. Zuccoli et al. (2010)

The only side effects of the diet the patient experienced included hyperuricemia and hypoproteinemia. Both issues were able to be corrected with modifications to oral intake. No adverse neurological effects were observed. It is also noted the patient was able to complete treatment without steroids. Steroid use tends to induce hyperglycemia and reduce apoptosis in tumor cells. Based on the outcome of this case, recurrence without compliance to a calorie restricted KD, researchers suggest a calorie restricted KD could be an effective adjuvant treatment for GBM in adults.

Strengths of this study include monitoring and reporting of the patient's oral intake. While one can assume biomarkers were assessed while the patient was on conventional therapy, these markers were not shared in the final report. A major weakness of this study is the patient's significant weight loss. A thirty pound weight loss occurred throughout the study, which likely involved muscle wasting. As discussed previously, wasting of LBM has been shown to have adverse effects for patients. To improve this study, body composition could have been assessed throughout the case. Although the results of this case are promising, it is only a case report of one individual. To further support the use of a CRKD for the management of GBM larger studies need to be completed, ideally with a control group to better support the intervention.

Another case report published by Schwartz et al. (2015) looked at the efficacy and feasibility of an CRKD as monotherapy in two glioma patients over a 12-week period. This study was completed as a registered clinical trial. The individuals included in the study were above the age of 18 with a GBM diagnosis. Both individuals had good performance status based on Eastern Cooperative Oncology Group (ECOG) criteria, anticipated life expectancy of more than three months and expression of ketolytic enzymes. Neither participant was on glycemic control medications nor glucocorticosteroids, had a recent history of cholecystectomy, presence of another primary malignancy, or required surgical or radiological intervention. Both patients had already progressed through available standard treatment. Following enrollment patients were admitted for 48 hours to follow a supervised fast to induce ketosis. Blood glucose and serum ketones were monitored. Next, the patients were provided diet education from a RD. Recommendations were made regarding daily protein, 0.6 grams/kilogram body weight, and

daily calories needs, 20 to 25 calories/kilogram ideal body weight with a 20 percent restriction. Patients were instructed to consume a 3:1 fat to carbohydrate and protein ratio. RD follow up continued twice weekly through the study period. Following discharge, patients were instructed to measure their blood glucose and blood ketones at least twice per day along with daily self-weighing. Glucose and ketones were able to be measured simultaneously with a provided meter. Target ranges were 50-70 mg/dL for blood glucose and 3-8 mmol/L for ketones. Additional biomarkers assessed at baseline, week 6, and week 12 included complete blood count, chemical profile, lipids, and uric acid. These biomarkers were not published in the final article.

Patient one only completed four weeks of the protocol due to disease progression. Progression indicates a CRKD is not an effective monotherapy. While following research protocol the patient experienced an initial 6% weight loss followed by weight stabilization. Despite completion of the 12 week protocol, patient two also had disease progression. Patient two experienced undesirable changes in his lipid panel. Neither participant reported significant adverse effects. Researchers speculated both participants experienced disease progression due to their inability to maintain glucose levels between 50-70 mg/dL and varying expression of ketolytic enzymes in tumor tissue. Macronutrient breakdown of each individual's intake was not disclosed in the published study. Patient two had higher expression of these enzymes while patient one had decreased expression. Varying degrees of expression led researchers to conclude some malignant cells are indeed able to metabolize ketones for energy. Based on these two cases a CRKD is considered safe but it remains unclear which patients will benefit

from this monotherapy for treatment of GBM. Researchers also acknowledged it is unknown how much daily energy intake is needed to make this intervention effective.

Strengths of this study included the initial inpatient monitoring and education. Inpatient monitoring allowed researches to identify and correct any adverse effects if needed. Additionally, receiving education from an expert source increased the quality of the information being provided. Education from a RD also might be perceived as more credible than from other sources. One interesting weakness is that researchers chose not to publish the biomarkers collected. With a small sample size, further research remains needed.

A pilot study, registered as a clinical trial, completed by Rieger et al. (2014) aimed to determine the safety, tolerability, and efficacy of a KD in 20 patients with recurrent glioblastoma. Inclusion criteria were age greater than 18 years old, relapse ≥ 6 months after initial surgery, relapse ≥ 3 months after radiation, relapse during chemotherapy, no other reasonable therapeutic options, patient refusal of further conventional treatment and Karnofsky performance score (KPS) ≥ 60 percent. Length of the study was determined by disease progression which was assessed using MRI scans. Researchers established a KD as consumption of only 60 g of carbohydrates daily. Education was provided to patients prior to starting the intervention in the form of brochures and cookbooks. Calorie, protein and fat recommendations were not provided. A calorie restriction was deemed unethical by researchers. Self-monitoring of urinary ketones was completed 2-3 times per week. Biomarkers, blood glucose, hemoglobin A1c, and a full lipid panel, were only assessed prior to diet initiation and during the diet, although when was not defined. Response to the intervention was assessed with MRI scans at 6-8 weeks or sooner if a participant was showing clinical signs of

progression. Protocol allowed participants to continue on the diet while salvage therapy was initiated. Salvage therapy was not defined further. Tolerability of the diet was assessed using a non-validated questionnaire about possible side effects of the diet such as diarrhea, constipation, hunger, and demand for glucose.

Of the 20 patients enrolled in the study, three patients discontinued the diet due to intolerability or perceived decreased quality of life. Results of seventeen patients were therefore evaluated for efficacy. All patients progressed on the diet alone. After progression eight participants elected to start salvage therapy while nine participants stopped the diet and declined further treatment. Average time to progression while on the diet was five weeks. Median survival time once the diet was initiated was 32 weeks. Thirteen patients submitted results for regular urine ketone analysis. Of these patients, 92% achieved ketosis at some point, but only 73% were in a state of stable ketosis defined as an average level of ketone bodies >0.5 mmol/L. The participants who achieved stable ketosis (n=8) had longer progression free survival (6 weeks) compared to participants who did not achieve stable ketosis (n=5, 3 weeks). The time difference between these groups was not statistically significant (p=0.069). Within the published study researchers utilized Kaplan-Meier analysis to assess progression free survival in patients who received Bevacizumab while on the KD (n=7) compared to another cohort receiving Bevacizumab without the KD (n=28). Time to progression free survival was not statistically different between the two groups (p=0.38).

Average blood glucose for participants not on steroids before the intervention and after the intervention was 99±21.8 and 92±9.1 respectively. Average blood glucose of those on steroids was not significantly different, 97±19.1 and 90±9.3. There were no significant changes

in any biomarkers. Questionnaire results were available for 12 patients. No serious adverse effects of the diet were reported. There were minimal reports of gastrointestinal intolerance. Both hunger and appetence for sugar decreased after one week of diet compliance.

Researchers concluded an unrestricted KD was safe and feasible in recurrent GBM patients. Based on the progression of all study participants, the diet was deemed ineffective as a monotherapy in advanced stage GBM patients. When compared to a cohort, not enrolled in the study but also being treated at the same facility, on Bevacizumab on a regular diet there was no significant difference in progression free survival. Researchers hypothesize lack of support for the KD as a monotherapy in this study may be attributed to the inability to reduce glucose levels from the lack of a calorie restriction.

The sample size of this study is a strength considering the previously reviewed articles only had one and two participants. Despite being conducted as a clinical trial, this study had several weaknesses. In the published report, researchers did not state how education was provided to participants. Participants may not have been thoroughly educated on food sources of carbohydrates. Lack of consistency of when biomarkers were assessed is another weakness of the study. If participants were fasting versus fed this would have significantly impacted results. Additionally, tolerability surveys were not collected from all patients. This could indicate under reporting of symptoms. Researchers in this study placed patients on a carbohydrate restriction but did not provide education regarding fat intake. This could mean patients were simply following a low carbohydrate diet, not a true KD which may have impacted outcomes.

Solid tumors outside of the central nervous system.

While the KD initially sparked interest for it's use in patients with solid brain tumors, there has also been interest in its use in patients with solid tumors throughout the body. In a prospective observational pilot study, *Effects of the Ketogenic Diet on the Quality of Life in 16 Patients with Advanced Cancer: A Pilot Trial* (Schmidt, Pfetzer, Schwab, Strauss, and Kammerer, 2011), researchers aimed to investigate the tolerability of a low carbohydrate high fat (LCHF) diet in advanced tumor patients with no further established treatment options. Primary outcomes included the effects of this diet on quality of life, biomarkers. and course of disease. Participants were recruited from a hospital that was a part of the University of Wuerzburg, Germany. Individuals were eligible to participate in the study if they presented with a metastatic solid tumor-based cancer, had no other established therapeutic options available, had a measurable parameter for follow up, acceptable KPS score, and laboratory values within nearly normal limits. Laboratory values monitored during the study included C-reactive protein, glucose, hemoglobin A1c, lipid panel, liver function tests, renal function, and leukocyte counts. Primary care doctors or medical oncologists were responsible for sending laboratory information to researchers. Body weight was not assessed on all patients.

The 12-week study was conducted in three parts. Part one included diet education and initial assessment of biomarkers, part two was the 12-week intervention, and part three included completion of final questionnaires and reassessment of biomarkers. Part one provided participants with a diet manual covering background information. Main principles of the diet included limiting daily carbohydrate intake to 70 grams, ideally 20 grams per meal, twice daily consumption of liquid snacks to be taken in the morning and afternoon, and an emphasis on omega 3 fatty acids to combat cachexia. The liquid snack recommended was an oil-protein

shake that contained yogurt, protein powder, and a vegetable oil mixture. In the resources provided to patients, researchers encourage participants to, “calculate useable CHO only”. Urinary ketones were monitored daily by participants. Stable ketonuria was considered to be present if ketones were at least 0.5 mmol/L for more than half of the days. Quality of life was assessed using EORTC QLQ-C30 questionnaire at baseline and after the 12-week trial period.

Five of the 16 participants completed the full 12-week study protocol. Reasons for dropout included lack of compliance or death. Quality of life scores were low at the beginning of the study, which researchers attribute to all patients having advanced stage disease. Quality of life aspects that improved during the study included emotional functioning and insomnia. With compliance to the diet, participants with previously regular bowel movements complained of constipation while those with diarrhea reported normalized bowels. After the trial period, all five participants had stable disease. These participants had stable ketonuria throughout the study.

Biomarkers were not available for all participants either at study entry, completion, or both. After six weeks researchers found a significant positive decrease in LDL levels ($p < 0.01$). HDL levels also decreased, but significance was less than LDL changes ($p=0.02$). Serum triglycerides increased non-significantly throughout the study, possibly due to a lack of calorie restriction. Blood urea nitrogen (BUN) levels changed significantly but remained within normal limits (31.7 ± 12.6 to 37.8 ± 19.4 mg/dL, $p < 0.0001$). ALT and total leukocyte count also significantly improved. Weight was only assessed in seven participants, baseline and 6-8 weeks after the intervention was implemented. Average weight change was two kilograms ($p < 0.05$).

Although five had stable disease, researchers considered a LCHF diet to be only slightly feasible and were unable to comment on the influence of the diet on course of disease. Statistical evaluation of the effect of the diet on tumor progression was not feasible due to the low number of participants who completed the study and what researchers stated was a heterogeneity of the study population. It was acknowledged that in order for a participant to be compliant with this diet they must be able to prepare and eat meals unassisted. Not all end stage cancer patients may be able to complete these activities of daily living.

A major weakness of this study is the inconsistences of biomarkers and weight. Both blood parameters and weight were not assessed consistently on all study participants. Additionally, lab values or blood samples were sent to researchers. Primary care doctors or medical oncologists were responsible for sending this information in meaning there could have been differences in collection, storage, and analysis. Any statistically significant results from changes in biomarkers should therefore be interpreted with skepticism. Due to the low number of participants that were able to complete the study, inclusion and exclusion may be seen as a weakness of the study. Changes to either criteria group might have resulted in a larger group completing the full study. One strength of this study was the specifics of the education provided to participants. This is the only study reviewed where researchers specified they instructed patients on net carbohydrate consumption. Net carbohydrate consumption is a common principle of the KD.

Researchers at the Veterans Affairs Pittsburgh Healthcare System (Tan-Shalaby et al., 2016) conducted a 16-week long study to primarily assess the feasibility and safety of a Modified Atkins Diet (MAD) in advanced stage cancer patients. A secondary outcome of this

study was the effect of the diet on tumor stability utilizing changes in fluorodeoxyglucose (FDG) PET/CT imaging. Participant recruitment occurred in an outpatient clinic at the previously mentioned healthcare system. Individuals were eligible for the study if they were not receiving chemotherapy at time of enrollment and if ECOG was 0-2. Exclusion criteria included gout, kidney stones, active cardiac disease, cachexia, poorly managed diabetes (fasting blood glucose greater than 180 mg/dL), liver dysfunction (enzyme elevation three times the normal limit in those with liver disease or five times the normal limit in those without liver disease), renal failure, and known brain disease. Seventeen overweight male participants were enrolled in this study. Fourteen participants had progressed through available treatment options while three patients had not received any systemic therapy.

The MAD was defined by researchers as a daily oral intake of only 20-40 grams carbohydrates. Protein, fat, and total calorie recommendations were not provided. Educated was provided to participants at the beginning of the 16-week study. Education focused on grocery shopping and menu planning. If participants experienced worsening performance status, progression of disease, grade three weight loss, or were unable to maintain at least trace ketosis they were removed from the study. Data collection occurred at five points throughout the study, baseline, week four, week eight, week 12, and week 16. Anthropometrics assessed included height, weight, and blood pressure. Serum biomarkers included complete metabolic panel 14 and ketones (BHB values). Complete metabolic panel 14 included electrolytes, uric acid, renal, liver, and lipid panel. All laboratory draws occurred between 10:00 am and 12:00 pm. It was not specified if participants were fasting. The EORTC QLQ-C30

questionnaire was used to assess quality of life. FDG PET/CT imaging scans were completed at baseline, week four, week eight, and week 16.

Six participants were removed from the study due to lack of dietary compliance. Of the remaining 11 participants, only four completed the full length of the study. Three of the four continued the diet after the study. No significant adverse effects were observed throughout the study. Average weight loss during the study was 27 pounds. Weight loss and ($p<0.000108$) and BMI ($p<0.0004$) changes were significant. Researchers were unable to find any significance between weight loss and any biomarkers throughout the study. Results of this analysis were not even close to significant. In regards to BHB, none of the participants reached a level of ketosis considered to be therapeutic. Therapeutic ketosis would have occurred if participants reached a glucose ketone index (GKI) <1.0. GKI is the ratio of glucose over BHB at any given time established in one previous study. Once ketosis was achieved, ketone levels remained stable. Blood glucose levels and lipid panels for 94% of participants did not change significantly over the 16-week study period. Quality of life improved throughout the study in the following areas: cognitive functioning, gastrointestinal function, and insomnia. In terms of disease progression five participants had disease progression by week four while six participants had stable or improved disease. At eight weeks, five participants were again stable. At the end of the study, four participants, diagnosed with melanoma or lung cancer, remained stable. At the time of publication one participant remained alive without any evidence of disease.

Based on the results, researchers were able to conclude a MAD was feasible, safe, and well tolerated in advanced stage cancers. Statistical analysis was not able to be completed regarding the diet's effect on tumor growth due to a low number of participants. Therefore,

there were no conclusions drawn regarding the effect of the diet on disease progression. Researchers were initially concerned with malnutrition but then noted individuals who responded best to treatment had sustained a weight loss of at least 10%. This weight change was not defined as cachectic even though body composition was not analyzed in this study.

A significant strength of this study was the variety of primary malignancies included. Individuals with prostate, melanoma, head and neck, pancreatic, renal, and lung were included. Additionally, researchers evaluated a numbers of biomarkers to help better understand the effects of a KD on various systems in the body. It was not specified by researchers however if participants were fasting which is a weakness of the study. If biomarkers were assessed more often, such as ketones being assessed by participants on a daily basis, researchers may have been able to identify more obvious trends. Another weakness is the entire population being white males. This could have been due to the population at the facility the study was conducted at but it is odd there was no interest from female patients.

Authors of the study *Targeting Insulin Inhibition as a Metabolic Therapy in Advanced Cancer: A Pilot Safety and Feasibility Dietary Trial in 10 Patients* (Fine et al., 2012) aimed to determine feasibility, safety, and efficacy of a low carbohydrate diet in the adult oncology population. Inclusion criteria for participants included progression through at least two conventional therapies and ability to assess disease using PET-FDG scanning. Exclusion included BMI less than 20 kg/m^2, significant weight loss within three months of study enrollment, currently taking glycemic control medications, known intestinal obstruction, congestive heart failure, and elevated hepatic or renal function markers. Prior to implementation of the intervention, patients were provided written materials on the diet including recipes,

carbohydrate limits, and suggestions of premade keto compliant products. Daily carbohydrate intake was to be restricted to less than 5% of total calories. Patients then trialed the diet for two to three days to ensure compliance during the 28-day intervention period was plausible. A physical exam, anthropometric measures, biomarkers, and diet recalls were collected at baseline and then weekly throughout the study. Biomarkers assessed following an overnight fast were serum BHB, insulin, IGF-1, and IGF-2. FDG-PET scans were completed at baseline and on day 28. Response to intervention was assessed using the European Organization for Research and Treatment of Cancer (EORTC) criteria.

Ten patients with various primary tumors met exclusion and inclusion criteria. Diagnoses include colon, breast, lung, esophageal and gynecological primaries. Only five patients were able to complete the 28-day intervention, the remaining patients completed between 26 and 27 days. Researchers noted discontinuation of the intervention was not due to adverse effects in any instance. Based on weekly diet recalls, carbohydrate intake was 9.0% ± 0.7% of daily calories. This was above the 5% goal researchers recommended during education. With the diet all patients decreased daily calorie consumption leading to non-significant weight change ($p=0.08$). Ketosis in this study was evaluated using serum BHB only. Mean BHB concentration was 10.9±1.7 mmol/L. As anticipated, there was an inverse relationship between insulin secretion and BHB ($p=0.03$) and blood glucose ($p=0.004$). There was no significant relationship between insulin and IGF-1 or IGF-2. In regards to disease status, evaluated with FDG-PET imaging before and after the intervention, six patients had a positive response and four demonstrated progression of disease. Of the patients with a positive response, five patients had stable disease and one showed disease regression. Individuals with response to the

intervention achieved higher levels of ketosis (16.6±3.2) compared to those with disease progression (5.1±1.9, p=0.02). Calorie deficits and weight loss did not vary between either group.

Researchers concluded a carbohydrate restriction may result in disease stabilization in individuals who are able to achieve a high level of ketosis. Cancer types that responded to the intervention included fallopian tube, breast, colorectal, and lung. A consistent state of ketosis was associated with a positive response or disease stability in participants, while calorie deficit and weight loss were not indicating insulin inhibition may inhibit cancer progression. Participants were able to complete the study without any significant adverse effects indicating this intervention is safe and feasible in certain late stage cancer patients. Researchers note that not all patients would be appropriate for this intervention due to performance status.

A strength of this study was overall compliance to the intervention as evidenced by elevated BHB levels. This indicates researchers provided sufficient education prior to intervention despite being non-specific with total carbohydrate intake; grams per day was not defined. Consistent data collection was another strength. All patients completed scheduled assessments of biomarkers following an assumed overnight fast, weight change, and diet recalls were also evaluated per study protocol. The major weakness of this study was length of intervention. Researchers explain a four week protocol was selected based on previous studies showing response to chemotherapy in as little as a week with FDG-PET evaluation. With an intervention of only four weeks, it remains unclear if long term compliance to a very low carbohydrate diet is feasible. Similar to the previously reviewed studies, the sample size is also a weakness of this study. Further research with a larger sample size is indicated.

Effect on body composition.

In a recent prospective study published by Klement and Sweeney (2016), the impact of a KD during radiotherapy or radiochemotherapy on body composition was assessed. Patients enrolled in the study based on personal interest and ability to meet inclusion criteria. One patient was recruited by researchers in attempt to reduce unintentional weight loss. Researchers noted past data shows ketosis decreases urinary nitrogen losses and muscle mass breakdown in undernourished cancer patients. The intervention of this study, a KD, was self-administered by all participants. Nutrition education regarding the KD was provided once weekly from baseline to study completion. Patients were provided various handouts, menus, and a popular book on the KD for cancer. A KD in this study was defined as a carbohydrate intake less than 50 grams daily, 80% of calories were to come from fat. No instruction on protein intake was provided. A ketogenic oral supplement was available in instances of unintentional weight loss. To assess compliance to the diet researchers requested a two day food record. Researchers utilized bioimpedance analysis (BIA), a validated method, to assess body composition. Participants were asked to complete the BIA in a fasted state once a week throughout the study. Biomarkers assessed during the study, at baseline, once during treatment, and after treatment, included serum complete blood count, HDL, LDL, BHB, insulin, IGF-1, and thyroid stimulating hormone (TSH). Patients monitored and recorded their urinary ketones at home, though it was not specified how often. This study assessed quality of life using the EORTC QLQ-C30 questionnaire.

Final study population was only six participants. Primary tumor diagnoses and stage of disease varied. Length of time on the invention varied based on the participants predetermined

course of radiochemotherapy, 32 to 66 days. Based on diet recalls, daily energy intake varied from 1402-2796 calories with an average of 73% of calories coming from fat. This was a ketogenic ratio of less than 2:1. Study participants were unable to reach the 80% of calories from fat that researchers desired. Only one participant required prescription of a ketogenic supplement to stop unintentional weight loss. BIA assessments for two participants were considered inaccurate due to the presence of metallic parts in their bodies. Weight change in two patients was significant ($p<0.0001$, $p=0.03$). These same two patients experienced a significant decrease in fat mass during the study ($p=0.002$, $p=0.01$). The same individuals experienced a significant increase, in fat free mass ($p=0.0017$, $p=0.012$). The figure below summarizes statistically analyzed BIA measures for the four participants.

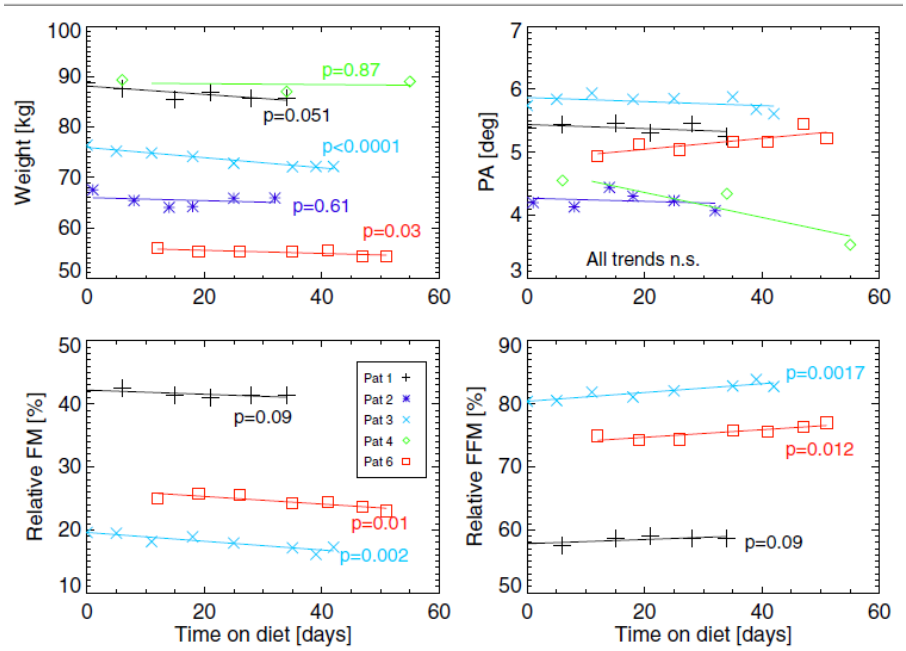


Figure 2 Klement & Sweeney (2016)

There were no notable trends in biomarkers assessed, except for BHB. There was however a significant negative correlation between BHB and glucose, as BHB increased glucose decreased

(Spearman's p=-0.35, p=0.05). Results of QOL questionnaire showed most participants were more satiated while following the KD compared to satiety reported prior to the invention. Two participants did report decreased appetite. In regards to response to therapy, five participants responded to treatment but this was expected due to staging. The individual with stage IV disease progressed while on the diet but progression was more significant when they transitioned to a regular diet.

Researchers concluded a KD may contribute to significant weight loss in patients currently undergoing radiotherapy or radiochemotherapy. This weight loss however is mostly fat mass. A KD in this small population preserved fat free mass based on BIA results. While undergoing conventional treatment for cancer, past research has shown progressive loss of lean body mass can lead to increased toxicities from treatment, worsened fatigue, and decreased quality of life. A diet that can help preserve muscle mass but reduce fat mass may improve tolerance to treatment but can also help reduce obesity after treatment for those with disease that can be cured. Obesity after treatment is a known lifestyle characteristic that increases risk of recurrence in a number of primary cancer types. No statements on the impact of the KD on disease progression were made as this was not a purpose of this study. Authors believe further research is warranted in this area. Researchers thought future research protocols should require participants to have more frequent counseling with a registered dietitian, provide oral supplements or meals, and offer cooking classes. These measures will help encourage compliance among participants.

Strengths of this study include using a validated tool to assess body composition. This was also the only study reviewed that looked at the use of the KD in patients with cancers that

were not defined as end stage. Weaknesses of this study included a small sample size. Sample size was further reduced due to exclusion of BIA results. Exclusion criteria to add to prevent enrolling inappropriate participants could be exclusion of those with metal implants. Additionally, it was odd that all participants in the study followed the intervention for varying amounts of time. Because of this discrepancy, lab values were collected at varying times which makes it difficult to compare results for significance between individuals.

Discussion

The first section of this review looked at the feasibility of the KD in patients with diagnosed GBM. The KD was used as monotherapy in some instances but was also used concurrently with standard treatment in other instances. In this population, researchers concluded a KD was safe and feasible. The length of these studies varied based on compliance to protocol or disease progression. Participants in these studies consumed anywhere from 10 to 60 grams of carbohydrates daily to induce ketosis. Ketones were monitored regularly throughout all studies. When a daily calorie restriction was included, as in studies conducted by Zuccoli et. al (2010) and Schwartz et al. (2015), most patients progressed slower than those without a calorie restriction, as in the study conducted by Rieger et al. (2014). A severe calorie of 600 calories per day was implemented in the Zuccoli et. al (2010) case study, which resulted in a significant weight change. Additionally, participants who were able to achieve significantly reduced serum blood glucose, seemed to have slowed or reduced disease progression. Unfortunately, blood glucose was not regularly monitored in all of the reviewed studies.

In the studies looking at the feasibility of the KD in patients with advanced stage solid tumors throughout the body, the diet was less feasible. The number of participants able to

complete study protocols was low. The duration of studies was short, ranging from four to 16 weeks. Factors that contributed to short length of intervention included difficulty with compliance, disease progression, or death. Three studies used the KD after other conventional treatments, conducted by Fine et al. (2012), Schmidt et al. (2011) and Tan-Shalaby et al. (2016), while one used the KD during standard therapy, Klement and Sweeney (2016). During standard therapy the author's goal was to evaluate the effect of the diet on body composition, not disease status. None of the studies reviewed used a calorie restriction. Daily carbohydrate intake varied from 20 to 70 grams or 9.0% of total daily calories. Participants with more stable urinary ketosis had a higher incidence of stable disease. Even though weight loss was sustained with a KD, this weight loss came from fat mass more often meaning the diet may have a desirable effect on preserving lean body mass. Studies looking at solid tumors other than GBM also looked at quality of life. Interestingly, despite difficulty with compliance, participants who were able to complete the studies reported increased quality of life largely due to improvements in emotional functioning and insomnia.

Conclusion

The evidence available regarding the efficacy of the Ketogenic diet in adult oncology is weak. Available evidence mostly evaluates the effect of the diet in patients who have progressed through conventional therapy and lacks a control group in all instances. Further research is needed to evaluate the effect of the diet in individuals with established treatment options but with overall low survival for stage IV disease, such as colon cancer. This research should include a control group.

Chapter 3: Proposal

The Ketogenic diet (KD) has been proposed as a metabolic approach to the management of malignancy however the number of studies investigating this intervention are lacking. The purpose of this study will be to investigate the effects of a KD on disease status in individuals with stage IV colon cancer on first line systemic therapy.

Study Design and Objectives

This will be a pilot randomized intervention study to primarily investigate if a KD combined with first line conventional therapy, Folfox, has a more significant impact on disease status assessed with fluorodeoxyglucose positron emission tomography (FDG-PET) imaging when compared to individuals on first line therapy alone over a 12-week period. Secondary aims are to examine the impact of a KD on biomarkers, quality of life and body composition, determine if the level of ketosis achieved is related to response to treatment, and determine if the presence of the ketolytic enzymes affects response to treatment.

Recruitment and Sample Size

The sample population evaluated in this study will be adults with stage IV colon cancer on first line chemotherapy. Subjects will be recruited from outpatient clinics at Midwestern Regional Medical Center, a facility owned and operated by Cancer Treatment Centers of America. If the enrollment period exceeds one year, individuals will be recruited from the existing four other Cancer Treatment Centers of America hospitals across the continental Unitd States. Inclusion criteria are: age over 18 years old, stage IV disease as defined by TNM staging, no past history of systemic chemotherapy, starting first line chemotherapy as recommended by the medical oncologist based on National Comprehensive Cancer Network (NCCN) guidelines,

and a subjective global assessment (SGA) score of A at time of enrollment indicating good nutritional status. Exclusion criteria are: insulin dependent diabetes mellitus, an SGA score of B or C which indicates malnutrition, Eastern Cooperative Oncology Group (ECOG) score greater than 2, patients already adhering to a strict KD and abnormal renal or hepatic function tests. As defined in previous feasibility studies, creatinine greater than 2.0 and liver function tests five times the normal limit in individuals with liver metastasis would be considered abnormal (Schmidt et al., 2011).

The sampling procedure for the study will be non-probability based. Individuals must voluntarily enroll in the study thus making random sampling unfeasible. The target sample size for the study is a total of 60 subjects. The intervention and control group will each consist of 30 individuals. Informed consent will be obtained at the time of study enrollment. Based on past intervention studies, attrition is expected to be 30%. Every other subject recruited will start the intervention protocol and the opposite subjects will be in the control group. The study will be started on a rolling basis, upon recruitment. At time of randomization individuals will be informed of the potential benefits of the KD to increase compliance to the intervention. Steps will be taken throughout the study to reduce attrition as further detailed below.

Intervention

Following enrollment and consent, participants in the intervention group will receive an hour of individualized diet education from a registered dietitian (RD) certified as a specialist in oncology (CSO). This will occur the same day as the first cycle chemotherapy is administered. Education provided to participants in the intervention group will include principles of the KD, individualized macronutrient needs, and if needed symptom management for gastrointestinal

issues that are currently occurring such as constipation or diarrhea. Resources provided to participants will include recipes, shopping lists, how to manage side effects of the diet, signs and symptoms of hypoglycemia and how to correct, and a handout with individualized macronutrient break down recommendations.

To determine macronutrient recommendations, first estimated energy needs will be calculated using predictive equations based on body mass index (BMI). For individuals with a BMI between 18.5-24.9 kg/m^2, estimated needs with be 25 calories per kilogram of body weight, BMI of 25.0-29.9 kg/m^2 21 calories per kilogram body weight, and BMI > 30.0 kg/m^2 14-18 calories per kilogram of body weight. Calorie estimates will be adjusted throughout the study if undesired weight loss or weight gain occurs. Macronutrient breakdown will follow a 3:1 ratio, or 3 grams of fat to 1 gram of carbohydrate and protein. This will provide an estimated 16 grams of net carbohydrates per 1,000 calories. Protein needs will be estimated at 0.6 grams/kilogram of body weight. No calorie restriction will be implemented.

Individuals in the control group will receive diet education from a RD using materials already available at the hospital. These materials largely focus on recommendations from the American Institute for Cancer Research (AICR) regarding diet and lifestyle. These individuals will also be provided counseling on symptom management, if needed.

Chemotherapy ordering will be completed by the participant's assigned medical oncologist. First line chemotherapy for advanced stage colon cancer per NCCN guidelines is a combination of Leucovorin Calcium, Fluorouracil, and Oxaliplatin. This regime is often referred to as Folfox and is recommended every two weeks. All three chemotherapies are administered intravenously. A bolus of Fluorouracil is administered with full doses of Leucovorin Calcium and

Oxaliplatin. Following this, a continuous infusion of Fluorouracil is administered for a target of 46-48 hours. Without any treatment interruptions, study participants should receive six cycles of Folfox during the 12-week intervention.

Data Collection

Data collection will occur at various points during the study (see timeline below). Assessment of ketolytic enzymes will be completed at the beginning of the study, within the first week of study enrollment. A biopsy of malignant tissue is needed to assess ketolytic enzymes. The primary tumor within the colon may have previously been removed, tissue from metastases can also be used. Within the first week of study enrollment would be desired. Tissue from this biopsy will be used by a pathologist to complete immunohistochemical staining to determine the presence of two major mitochondrial ketolytic enzymes, succinyl CoA: 3 oxoacid CoA transferase and beta-3-hydroxybutyrate dehydrogenase. Biopsies will be completed by a gastroenterologist during colonoscopy procedure. If a primary tumor is not present, an interventional radiologist will perform a biopsy of the metastatic site.

Quality of life.

To assess quality of life, the EORTC QLQ-C30 questionnaire will be used (The European Organization for Research and Treatment of Cancer, 2001). This is a tool that has been validated in the oncology population for assessing quality of life. Participants in the study will complete this questionnaire at day zero and then at the end of the 12-week intervention.

Body composition.

Body composition will be assessed three times during the study; at baseline, week six, and week 12. Body composition will be assessed using bioelectrical impedance analysis (BIA)

using the InBody 520 scale available at Cancer Treatment Centers of America Midwestern Regional Medical Center. BIA technology is a validated tool to assess body composition. Participants will be instructed to complete the BIA after an overnight fast. Minimal activity will be encouraged to increase accuracy of the test. The BIA results will be used throughout the study to assess adequacy of calorie and protein intake. Changes will be made to recommendations as needed with involuntary wasting of lean body mass.

Biomarker assessment.

A variety of biomarkers will be assessed throughout the day. To observe changes in lipid panel and hemoglobin A1c, these markers will be assessed at the beginning and the end of the study. Participants will have these labs assessed after an overnight fast. Since participants will be returning for chemotherapy every two weeks, a complete blood count, complete metabolic panel, serum insulin, and beta hydroxybutyrate will be assessed at these visits.

Urinary ketones will be monitored by patients daily at home. All participants will assess ketones. For the intervention group, the dietitian will be able to review patient's ketone logs at the scheduled biweekly visits to insure a consistent state of ketosis. Since published studies are limited, it is unclear if self-monitoring urinary or serum ketones is more accurate. To increase compliance, participants will assess urinary ketones. Individuals may be uncomfortable assessing serum levels at home. Urinary ketones will be assessed at home using over the counter Ketostix produced by Bayer. These strips assess the presence of acetoacetate when passed through the urine stream. The user then compares the color of the strip to the color chart provided to determine level of ketosis. Urinary ketones should be greater than 0.5 mmol/L. A 2016 study completed by Urbain and Bertz established the best time of day to assess

urinary ketones is in the morning after an overnight fast or postprandially in the evening. Ketone logs will be submitted at each clinic visit.

Disease status.

Status of disease will be assessed using computed tomography (CT) or magnetic resonance imaging (MRI) of the chest, abdomen, and pelvis as per NCCN guidelines. In this study, disease will also be assessed using fluorodeoxyglucose positron emission tomography (FDG-PET) imaging. FDG-PET looks specifically at metabolic activity of tissues. On the scan itself, any areas of the body where glucose uptake is high will show more increased metabolic activity indicating cells that are using glucose for energy. FDG-PET scans are more specific than MRI or CT scans. The medical oncologist would be responsible for ordering FDG-PET scans. A radiologist would read the scans using the RECIST criteria to evaluate extent of disease. RECIST criteria is utilized currently by the radiology department at the participating hospital to assess response to therapy.

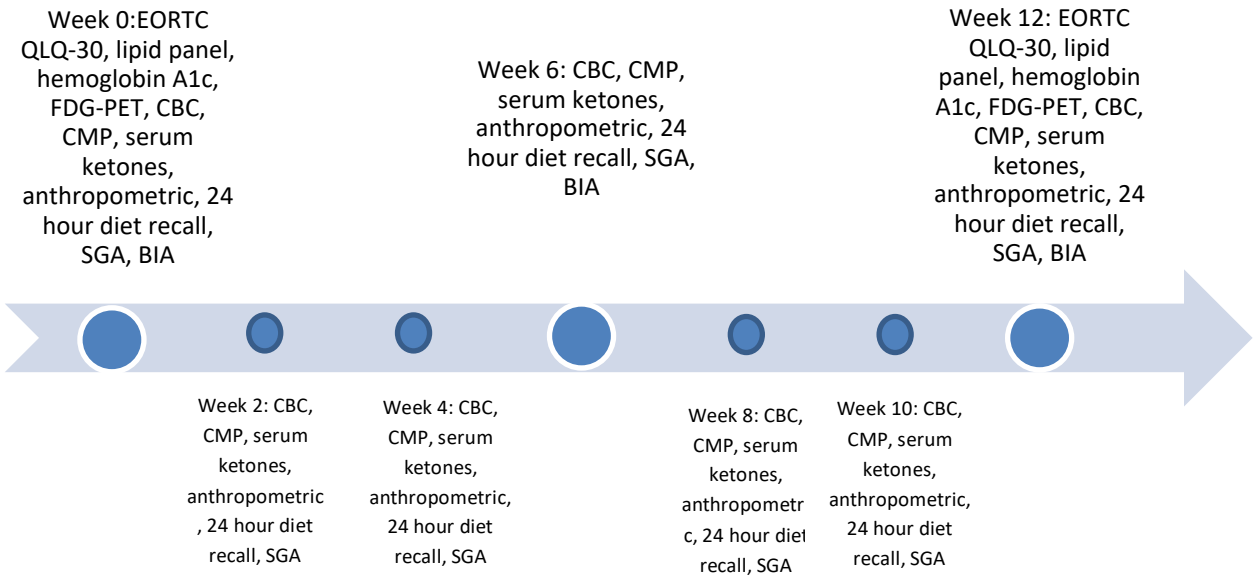
Survival will be assessed during the 12-week course of the study and for 12 months following study completion. Individuals who respond to the intervention will be encouraged to follow the KD following study completion as well.

Nutrition support and assessment.

At each biweekly clinic visit, participants in the intervention group will have a follow up visit with a RD. At this time, study participants will be required to provide a 24-hour diet recall to be assessed for compliance to the intervention. Participants will be encouraged at study initiation to track diet recalls in an application for mobile devices, Carb Manager, to increase accuracy of recalls but also compliance. Nutrition counseling will be provided as needed taking

into account ketone levels, weight change, and macronutrients consumed per the diet recall. The SGA will be completed at each visit to note any changes in nutritional status. Participants will be provided encouragement and praise to help with compliance to the intervention as well as recommendations for symptom management such as nausea or constipation, if needed.

Individuals in the control group will meet with a RD as needed throughout the 12-week study. The same biomarkers, anthropometric measures, and response to treatment will be completed on these individuals. Those who meet with the RD will be asked to provide a verbal 24-hour recall. The timing of data collection is summarized in the chart below.



Data Analysis

Data will be collected and recorded by the primary researcher of the study. Data will be stored in a password protected Excel file. In the file participants will be associated only with medical record number not name. Once all data values are collected statistical analysis can be conducted. A paired t-test and repeated measures ANOVA will be used for within group

comparisons on changes in lipids and HbA1c. Linear regression will also be conducted to assess the relationship between level of ketosis and response to treatment. Kaplan-Meier estimate will be conducted for survival analysis. All statistical analysis would be completed using SPSS software, with a $p<0.05$ level of significance.

Chapter 4: Discussion

The main objective of this study protocol developed is to determine whether compliance to a KD increases sensitivity to first line therapy in stage IV colon cancer patients. This study will be unlike currently published studies because there will be a control group. Inclusion of a control group will determine if the results are due to the diet intervention. In the currently available literature, response of colon cancer patients to the Ketogenic diet has been varied, making it difficult to identify whether the Ketogenic diet is an effective therapeutic option.

Study Design

A controlled trial was selected as the design since it is best for identifying whether an intervention is effective. The length of the study, 12 weeks, was determined based on National Comprehensive Cancer Network guidelines for the treatment of colon cancer. Within the 2018 guidelines, it is advised disease status is evaluated every three to six months. For stage IV patients, the study population, NCCN guidelines encourage evaluation of disease sooner than 6 months (National Comprehensive Cancer Network, 2018**)**. In the clinic where the study will be conducted, the medical oncologists will evaluate disease every 12 weeks.

Stage IV colon cancer patients were selected as the study population for a number of reasons. Within the United States, colorectal cancers are the fourth most commonly diagnosed primary tumors. Since this is a commonly diagnosed cancer, recruitment within the outpatient clinic at Cancer Treatment Centers of America Midwestern Regional Medical Center will be feasible. The desired sample size for the study, will be 60 participants to be distributed equally between intervention and control groups. While a larger sample size would have more clinically

significant results, the sample size was kept small to allow for hopeful completion of the proposed study in the future. Additionally, finding participants willing to enroll in such as study may be difficult. A smaller sample is more realistic. Survival rates for metastatic colon cancers are overall low. The five-year survival rate is around 20% (Surveillance, Epidemiology and End Results (SEER) Program, 2011-2015). This makes additional treatment options, such as the Ketogenic diet, more desirable to hopefully increase survival rates in the future. Malnutrition is a risk for all metastatic cancer patients. Due to the location of the primary tumors and common hepatic metastases, all patients with gastrointestinal primary cancer are considered high nutritional risk. However, there is a limited number of studies that have shown individuals with colon cancer are not often hypermetabolic. Additionally, compared to other gastrointestinal primary tumors such as pancreatic cancer or gastric cancer, a colon tumor does not alter normal digestion as significantly. Individuals with a pancreatic tumor often require pancreatic enzyme replacement therapy to assist in digestion, largely fat digestion. Gastric primary individuals may struggle with satiety more due to tumor location. A high fat diet such as the Ketogenic diet, therefore might be poorly tolerated in these individuals.

For the intervention, it was ultimately decided to not implement a calorie restriction in this study protocol because unless the restriction was well below normal metabolic needs, such as in the case study published by Zuccoli et al. (2010) where the individual consumed only 600 calories daily, it did not seem to impact response to intervention. However, participants of the proposed study may naturally reduce calorie intake due to the satiety experienced while on a Ketogenic diet. Nutrition counseling will be provided by a registered dietitian every two weeks. Counseling will be offered every two weeks since this is how often participants will be returning

to the clinic for scheduled systemic therapy per NCCN guidelines (National Comprehensive Cancer Network, 2018) and since the intervention group will likely need intensive support to maintain the diet. The registered dietitian (RD) will also hold the Certified Specialist in Oncology (CSO) board certification to ensure the RD is well versed in the unique needs of the adult oncology population.

Anticipated Results

Since macronutrient recommendations will be more individualized (as a ratio within estimated needs), it is anticipated that the response to the intervention, in terms of disease size at the primary site and metastatic sites assessed with FDG-PET imaging, will be more significant than in past studies. In the studies that evaluated the positive effects of the Ketogenic diet on solid tumors outside of the central nervous system, it seemed more rigid and detailed diet guidelines such as within this proposal, were more effective for controlling disease. The intensive support should improve compliance compared to past studies. The diet intervention specifies 6% of calories from carbohydrates, or roughly 16 grams per 1000 calories. This proportion of carbohydrates is based on a 3:1 ketogenic ratio. Studies conducted evaluating the use of the Ketogenic diet for pediatric epilepsy have traditionally used a 4:1 or 3:1 ratio (Vitaflo, n.d.). A 4:1 ratio, is extremely restrictive and would likely decrease compliance in the proposed study. In the studies by Fine et al. (2012) and Tan-Shalaby et al. (2016), a lower carbohydrate goal was associated with more positive response. The authors of Fine et al. (2012) suggested this response is more likely due to decreased insulin secretion leading to higher level of ketosis. In the Tan-Shalaby et al. (2016) study, authors did not evaluate if the level of ketosis from better compliance to a diet with only 20-40 grams of carbohydrates impacted positive

outcomes. All four participants who completed the full length of this study had stable or partially improved disease status. In the proposed study, more frequent and consistent monitoring of both serum and urinary ketones will help to determine if the extent of ketosis impacts outcomes. Past studies considered stable ketonuria as urinary ketones being present at greater than 0.5 mmol/L (Rieger et al., 2015; Schmidt et al., 2011). It is anticipated will compliance and monitoring of the proposed intervention, participants will be able to at least achieve this level of ketosis. Disease free survival within the study period will not be anticipated in any participants due to the lack of past studies documenting benefit of the Ketogenic diet. One reason for dropout during the study could be mortality due to malignancy.

Tumor expression of ketolytic enzymes will also be assessed in the proposed study to help determine if the expression of these enzymes will determine response to treatment. Individuals with higher expression of 3-oxoacid CoA transferase and beta-3-hydroxybutyrate dehydrogenase will likely not respond to the intervention as well or at all due to the tumors ability to metabolize ketones for energy.

Secondary objectives of the proposed study include effect of the Ketogenic diet on biomarkers, body composition, and quality of life, and if the presence of ketolytic enzymes impacts response. Of those published studies where quality of life was assessed, improvements were self-reported by participants. Improved quality of life in the intervention group is also anticipated as a result of the proposed study.

Interestingly, in most of the previous studies conducted, there were not significant changes in biomarkers. Rieger et al. (2014) and Tan-Shalaby et al. (2016) both concluded no significant changes in biomarkers including lipid panel and fasting blood glucose. Errors or

inconsistencies in data collection might have contributed to lack of significant changes. In the proposed study, decreased hemoglobin A1c is anticipated due to consistent assessment and regular diet education. Based on metabolism, it is only logical decreased carbohydrate intake would reduce serum blood glucose. The study published by Schmidt et al. (2011) reported significant decreases in LDL cholesterol. In a review published in 2013, it is stated there have been studies conducted to show reductions in LDL cholesterol when using a Ketogenic diet for cardiovascular disease (Paoli et al., 2013). With this information in mind and encouragement of a focus on unsaturated fatty acids, positive changes in LDL cholesterol are anticipated. Schmidt et al. (2011) also reported improvements in a specific liver enzyme, ALT. This result would be hoped for considering many stage IV colorectal patients have hepatic impairment due to metastatic disease.

While following the study protocol, weight loss will be anticipated at first followed by a plateau. This is characteristic of what occurs with glycogen depletion when following a low carbohydrate diet. Weight lost, will be fat mass versus fat free mass, consistent with the results of a 2016 study by Klement and Sweeney. In this study, when body composition was evaluated during radiochemotherapy using BIA technology, participants lost a statistically significant amount of weight, but most of this weight was fat mass versus fat free mass. These results suggest a Ketogenic diet might help to preserve lean body mass in cancer patients which is desired to decrease cachexia development. While not all the patients in the referenced study had stage IV disease, it is hoped the same results will occur in the proposed study. Muscle wasting during cancer treatment can have very detrimental effects for patients.

In all of the published studies where quality of life was assessed, improvements were reported by participants. Thus, it is expected that subjects in the intervention group will experience an increase in quality of life.

Potential Difficulties

Potential difficulties with the proposed study will start with enrollment and continue throughout the length of the study with compliance to the intervention. To increase enrollment, potential participants will be provided brief education regarding the proposed benefits of the intervention as seen in past studies. Positive results such as quality of life will be highlighted. A strict Ketogenic diet is difficult for healthy individuals to remain compliant to, and cancer patients often have even more barriers present that may make meal preparation or choices difficult. Multiple measures will be taken to ensure compliance as much as possible throughout the 12-week intervention. The patient's primary caregiver will also be provided education regarding meal preparation and portion sizes. Patients will be required to meet with a registered dietitian every two weeks to review a diet recall but also symptom management as needed to manage any chemotherapy associated barriers to eating. The diet recall patients provide must be logged into a specified application for accuracy. The dietitian will also review ketone logs. Patients who are regularly not in ketosis or those that submit an undesirable recall will be contacted by phone one week later. They will be asked to submit another diet recall at this time. Consistently non-compliant patients may need to withdraw from the study.

Another possible difficulty will be if patients do not receive treatment as scheduled. Treatment can be delayed by the medical oncologist due to poor performance status, insufficient blood counts, or patient preference. If treatment is held at any point during the

study period, it will have to be documented and factored into the results. Patients who skip a treatment might have a decreased response to treatment. Traditionally, patients are given steroids with chemotherapy infusions to reduce side effects. It would be ideal for the medical oncologist to not order steroids due to their negative effects on glycemic control, however if the physician deems this is needed, again researchers will have to take that into consideration when interpreting results. It would be interesting to see if those that receive steroids have a less significant response to treatment and if in turn, decreased glycemic control is also seen.

Practice Implications

Results of the proposed study will have significant applications to practice, regardless of the results. The cancer epidemic has continued to grow over the last few decades and this pattern will likely continue. There is a large volume of research available regarding diet before diagnosis to hopefully prevent an initial diagnosis and diet after treatment to prevent recurrence. The gap that exists in the literature is how an RD is to instruct patients during treatment if they are maintaining good nutritional status, and if it's feasible. The Ketogenic diet has gained interest in humans due to positive results of cell studies. These cell studies are also the crux of the theory that "sugar feeds cancer". A quick online search regarding the diet for cancer will produce many a large non-reliable web pages urging patients to avoid any and all sources of carbohydrates. This thought process can often stimulate a fear of food for patients who need a nourishing diet to be able to receive the treatment they desire. If the proposed study therefore does not show any benefit to following a rigid low carbohydrate diet, it can be used as evidence to debunk the "sugar feeds cancer" myth.

On the other hand, if the proposed study does show benefit for the use of a Ketogenic diet during chemotherapy, it will help to fill that gap in the literature. Those with a positive response to the intervention, would be encouraged to continue the diet after the 12 week period. Cancer patients are often looking for guidance on what they can do to improve their response to therapy. While the Ketogenic diet is an intensive approach to impacting outcomes, it is feasible. It is also hoped, showing benefit of specific nutrition intervention will show the value of nutrition to other healthcare providers. The proposed study will only be looking at stage IV colon cancer patients. If the intervention does have positive outcomes, the Ketogenic diet can be tested in other primary malignancies, such as those with low survival rates. This will also be the first study published with a control group, making the hopefully positive results more useful.

Opportunities for Future Research

Even with the completion of the proposed study and the articles previously referenced within the literature review, there may still remain a paucity of studies on the use of the KD in patients with cancer; the largest limitation of these studies is the relatively low number of study participants. Conclusions from the literature review are that the KD can be incorporated as part of treatment for advanced stage oncology patients, but there is not enough convincing evidence to recommend this diet to all oncology patients. The KD itself would take a significant amount of work from the patient, support from caregivers, and regular education from medical professionals. The KD was found to be feasible in most populations. Future research should evaluate this therapeutic diet in individuals at high risk for malnutrition. While a reasonable calorie restriction does not seem to impact progression of disease, a significant calorie

restriction as seen in the case study published by Zuccoli et al. (2010), and a clinically significant weight loss as seen in the study by Tan-Shalaby et al. (2016), seemed to be beneficial for patients. Current nutritional recommendations for high risk oncology patients do not encourage either of these strategies. Additionally, some researchers argue limiting calorie intake is unethical in oncology patients.

The variability of the prescribed diets among the current literature makes it difficult to translate findings into practical recommendations. Daily carbohydrate allowance varied from 10 to 70 grams and specific recommendations related to fat intake were not provided in any of the studies. The proposed study protocol aims to better define macronutrient breakdown. Schmidt et al. (2011) argued a higher carbohydrate intake maybe be consumed while maintaining a state of ketosis due to "increased rates of gluconeogenesis which burn the body's lean mass". Further research is needed in regard to tolerable and beneficial carbohydrate, calorie intake, and macronutrient breakdown. Protein needs remain very unclear.

Further research is needed prior to using the KD in practice on mechanisms of action, what biomarkers must be monitored regularly, methods to identify responders versus non-responders, when the intervention is most beneficial, and if a calorie restriction is needed for efficacy. Schwartz et al. (2015) evaluated participant's GBM tumors for expression of two mitochondrial ketolytic enzymes, 3-oxoacid CoA transferase and beta-3-hydroxybutyrate dehydrogenase. Each participant had different expression of these enzymes. Ketolytic enzymes were not assessed in other studies looking at solid tumors throughout the body, but this could have been why certain tumors responded while others did not. Like immunotherapy, evaluation of these enzymes might be indicated prior to recommending the KD to patients. All studies

reviewed had participants self-monitor urinary ketones, while few studies required regular blood glucose monitoring. The basis of the KD is that tumors depend on glucose (Schmidt et. al, 2011). Theoretically, if blood glucose is lower, tumor activity should be reduced as well. What is unclear is the optimal blood glucose range that should be maintained and if this is feasible considering medications patients are taking. Participants in the study conducted by Schwartz et al. (2015) were unable to maintain low blood glucose levels which may have contributed to disease progression. Tan-Shalaby et al. (2016), also discuss the Glucose/Ketone Index (GKI) which is "when tumor growth is expected to slow or cease". No participants in their study achieved this.

From the available resources it can be concluded, prior to recommending the KD in clinical practice to increase sensitivity to conventional therapy or as a monotherapy in patients with central nervous system tumors or other solid tumors throughout the body, a number of variables need to be further researched. Patients interested in following the KD should be informed the evidence is limited making it difficult to justify such an immense change to their current dietary pattern.

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Appendix A:

Mount Mary University
Institutional Review Board (IRB)
for the Protection of Human Subjects

Application for IRB Review

DATA COLLECTION CANNOT BEGIN
UNTIL THE IRB HAS APPROVED THIS PROJECT

Directions:

- Faculty and student researchers, as well as student research advisors, should **read all relevant information on the University IRB page in My Mount Mary before initiating an application**. This includes full knowledge of the US Department of Health and Human Services Code of Federal Regulations Title 45 (Public Welfare), Part 46 (Protection of Human Subjects). http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.html
- All applicants must verify completion of Human Subjects Training. See http://www.citiprogram.org
- The IRB application must be filed and approved by the IRB **prior** to any Mount Mary University faculty, staff, or student (undergraduate or graduate), initiating a research project/study.
- If there is a cooperating institution, attach a copy of their IRB approval.
- In the case of a student research project, the student may complete the IRB application but the student's research advisor must sign and submit the application to the IRB for approval. It is the responsibility of the faculty research advisor to ensure that student applications and all attachments (e.g. informed consent forms and survey instruments) are in their final edited form. Even though a student research project may qualify as **exempt** from full IRB review, the research advisor may request the student to complete and submit a full IRB application.
- Complete this application using your word processing program (ex. Word), then print it out and obtain signatures from all investigators and advisors. (**Handwritten applications will not be accepted**.) For your benefit, save the completed application on your computer in case it needs to be revised and resubmitted.
- This is a professional document; please check spelling, grammar and punctuation.
- Submit a hard copy of the completed application with required signatures and attachments to Tammy Scheidegger, IRB Chair, Counseling Department. **(Emailed applications will not be accepted.)**
- Allow a **minimum of 10 working days** to process your application. Make sure this time frame is accounted for when considering initiation of data collection and due dates for student projects.

- For class projects you must submit IRB applications to the IRB Chair by October 31st of the fall semester and March 31st for the spring semester. For summer classes, please consult with the IRB Chair.
- Upon receipt of the IRB letter of approval, data collection may begin.

I. Required Documentation **(No action will be taken without these attachments.)**

Are the following attached to the IRB application?

Consent application	X☐ Yes	Applications should include explanation of procedures, risk, safeguards, freedom to withdraw, confidentiality, offer to answer inquiries, third party referral for concerns, signature and date. See Appendix.A.
Questionnaire/Survey Instrument(s)	X☐ Yes	If survey is being conducted verbally, a copy of the introductory comments and survey questions being asked must be attached to this application. If survey includes focus group questions, a complete list of the question should be attached. For research using a published/purchased instrument, a photocopy of the instrument will suffice.
Verification of Human Subjects Training	X☐ Yes	Copy of transcript, certificate or other evidence .
Copy of cooperating institution's IRB approval.	X☐ Yes	Not required if there is no cooperating institution. .

II. Investigator(s):

Name: Danielle Hill Phone: 848-308-6533
Affiliation with Mount Mary University (e.g. faculty, student, etc): Student
Email: hill.danielle19@gmail.com

Signature: _____ Date: 7/22/2018

If student, list Research Advisor and complete Section II. Research Advisor must provide requested information and verify.

Department: Dietetics

Research Advisor's Name: Megan Baumler
Email: baumlerm@mtmary.edu Phone: 414-443-3659

Research Advisor: Have you completed Human Subject's Training? ☐ Yes ☐ No

Research advisor's signature indicates responsibility for student compliance with all IRB requirements.

Signature: Date:

_____
Research Advisor

III. Project Description

Instructions: Briefly describe the proposed project including the sample and methodology (e.g. human subjects, data collection, data analysis and instruments).

1) Objectives (purpose of project):

The objective of this project is to determine how the Ketogenic diet affects response to first line treatment in individuals diagnosed with stage IV colon cancer compared to individuals who follow the standard Western diet while also on first line therapy.

2) Relevance to practice/body of knowledge:

The Ketogenic diet is promoted in many online communities and forums as an alternative treatment for cancer based on anecdotal accounts of individuals. What separates the Ketogenic diet from other anecdotal diet approaches to the treatment of cancer is published cell and animal studies showing benefit to this intervention. In humans, a limited number of feasibility studies have been conducted evaluating the effect of the diet in late stage oncology patients who have declined conventional therapy or have progressed through available treatment options. To date, there are no studies published looking at the effects of the Ketogenic diet on disease status in those with stage IV colon cancer on first line therapy compared to a control group. More research evaluating if the diet intervention impacts disease status is needed.

3) Describe the research design (e.g. subject/participant selection and assignment, design, intervention, data analysis):

This will be a randomized intervention study with a desired population size of 60 total participants. Subjects will be initially randomized to a control or intervention group. The control

group will follow a standard Western diet. The intervention group will follow a Ketogenic diet with a desired carbohydrate intake of only 6% of total daily caloric intake. Length of the study will be twelve weeks. Studies will be recruited from the outpatient oncology clinic at Cancer Treatment Centers of America Midwestern Regional Medical Center. The study will be limited to individuals aged over 18 years old, diagnosed with stage IV disease as defined by TNM staging, no past history of systemic chemotherapy, starting first line chemotherapy as recommended by the medical oncologist based on National Comprehensive Cancer Network (NCCN) guidelines, and a subjective global assessment (SGA) score of A at time of enrollment indicating good nutritional status. Excluded individuals will include those with insulin dependent diabetes mellitus, a SGA score of B or C which indicates malnutrition, Eastern Cooperative Oncology Group (ECOG) score greater than 2, patients already adhering to a strict Ketogenic diet and abnormal renal or hepatic function tests. After enrollment and consent, participants in the intervention group will receive an hour of individualized diet education from a registered dietitian (RD) certified as a specialist in oncology (CSO) the same day as the first cycle of chemotherapy is administered. Education provided to participants in the intervention group will include principles of the Ketogenic diet, individualized macronutrient needs, and symptom management for currently present gastrointestinal issues. Resources provided to participants will include recipes, shopping lists, how to manage side effects of the diet, signs and symptoms of hypoglycemia and how to correct, and a handout with individualized macronutrient break down recommendations. To determine macronutrient recommendations, first estimated energy needs will be calculated using predictive equations based on body mass index. For individuals with a BMI between 18.5-24.9 kg/m^2, estimated needs with be 25 calories per kilogram of body weight, BMI of 25.0-29.9 kg/m^2 21 calories per kilogram body weight, and BMI > 30.0 kg/m^2 14-18 calories per kilogram of body weight. Calorie estimates will be adjusted throughout the study if undesired weight loss or weight gain occurs. Macronutrient breakdown will follow a 3:1 ratio, or 3 grams of fat to 1 gram of carbohydrate and protein. This will provide an estimated 16 grams of net carbohydrates per 1,000 calories. Protein needs will be estimated at 0.6 grams/kilogram of body weight. No calorie restriction will be implemented. Individuals in the control group will receive diet education from a RD focusing on recommendations from the American Institute for Cancer Research (AICR) regarding diet and lifestyle. These individuals will also be provided counseling on symptom management if needed. Chemotherapy will be ordered by the participants medical oncologist. First line chemotherapy for advanced stage colon cancer per NCCN guidelines is a combination of Leucovorin Calcium, Fluorouracil, and Oxaliplatin. This regime is recommended every two weeks. All three chemotherapies are administered intravenously. Without any treatment interruptions, study participants should receive six cycles of Folfox during the 12 week intervention. Data collection will occur at various points during the study. Assessment of ketolytic enzymes will ideally be completed at the beginning of the study. Tissue from this a biopsy obtained by a gastroenterologist during a colonoscopy will be used by a pathologist to complete immunohistochemical staining to determine the presence of two major mitochondrial ketolytic enzymes, succinyl CoA: 3 oxoacid CoA transferase and beta-3-hydroxybutyrate dehydrogenase. To assess quality of life, the EORTC QLQ-C30 questionnaire will be completed by participants at baseline and week 12. Body composition will be assessed three times during the study, at baseline, week six, and week 12. Body composition will be assessed using bioelectrical impedance analysis (BIA) using the InBody

520 scale. Participants will be instructed to complete the BIA after an overnight fast. The BIA results will be used throughout the study to assess adequacy of calorie and protein intake. Changes will be made to recommendations as needed with involuntary wasting of lean body mass. A variety of biomarkers will be assessed throughout the day. To observe changes in lipid panel and hemoglobin A1c, these markers will be assessed at the beginning and the end of the study. Participants will have these labs assessed after an overnight fast. Since participants will be returning for chemotherapy every two weeks, a complete blood count and complete metabolic panel will be assessed at these visits. Serum insulin will be assessed in all participants. The serum ketone, beta hydroxybutyrate, will be added to blood draws for the intervention group. Urinary ketones will be monitored by patients daily at home. Urinary ketones will be assessed at home using over the counter Ketostix produced by Bayer. These strips assess the presence of acetoacetate when passed through the urine stream. The user then compares the color of the strip to the color chart provided to determine level of ketosis. Urinary ketones should be greater than 0.5 mmol/L. Ketone logs will be submitted at each clinic visit. In this study, it would be more ideal for patient's disease status will be assessed using fluorodeoxyglucose positron emission tomography (FDG-PET) imaging. FDG-PET looks specifically at metabolic activity of tissues. FDG-PET scans are more specific than MRI or CT scans. The medical oncologist would be responsible for ordering FDG-PET scans at baseline and week 12. A radiologist would read the scans using the RECIST criteria to evaluate extent of disease. RECIST criteria is utilized currently by the radiology department at the participating hospital to assess response to therapy. At each two week clinic visits, participants in the intervention group will have a follow up visit with a RD to review at least one 24 hour diet recall entered into the Carb Manager application. Nutrition counseling will be provided as needed taking into account ketone levels, weight change, and macronutrients consumed per the diet recall. The SGA will be completed at each visit. Participants will be provided encouragement and praise to help with compliance to the intervention as well as recommendations for symptom management. Individuals in the control group will meet with a registered dietitian as needed throughout the 12 week study. The same biomarkers, anthropometric measures, and response to treatment will be completed on these individuals. Monitoring of urinary ketones is not necessary to assess within the control group since on a regular diet ketones should not be present. A paired t-test and repeated measures ANOVA would be used for within group comparisons on changes in lipids and HbA1c. Linear regression will also be conducted to assess the relationship between level of ketosis and response to treatment. All statistical analysis would be completed using SPSS software.

4) What measurement/data collection tools are being used?

24 hour diet recall recorded on the Carb Manager application (Wombat Apps LLC, Washington, USA), Subjective Global Assessment, EORTC QLQ-C30 questionnaire (EORTC Quality of Life Department, Brussels, Belgium), InBody 520 scale, biomarkers through blood samples, urinary ketones with Ketostix produced by Bayer, RECIST criteria (PAREXEL International Corporation), expression of ketolytic enzymes with immunohistochemical staining

Is the proposed project "research" as defined by Institutional Review Board requirements?

- Research is defined as a systematic investigation, including research development, testing and evaluation, designed to develop or contribute to generalizable knowledge.
- A human subject is defined as a living individual about whom an investigator obtains either 1) data through intervention or interaction with the individual; or 2) identifiable private information.

Does the research involve human subjects or official records about human subjects?

X☐ Yes
☐ No

***If NO STOP here and SUBMIT application*.**

If the results will be available in the library, presented at a professional conference (includes any presentation to group(s) outside of the classroom), or published, please check the Yes box:

X☐ Yes
☐ No

If the YES box is CHECKED, proceed to SECTION IV.

***If the NO box is CHECKED, STOP here and SUBMIT application*.**

IV. Exemptions

Are you requesting exemption from IRB review in one of the federally approved categories? If yes, please reference OHRP website http://www.hhs.gov/ohrp/humansubjects/guidance/45cfr46.html and continue with application.

1) Does the research meet the criteria for exempt category 1 (education)? [45 CFR 46.101 (b) (1)]

Is the research conducted in established or commonly accepted educational settings (e.g. schools, Universities or other sites where educational activities regularly occur)? ☐ Yes X☐ No

Does the research study involve only normal education practices (e.g. instructional strategies, techniques, curricula, or classroom management techniques)? ☐ Yes X☐ No

*If **both** questions are answered **yes**, stop here, proceed to **Section I Required Documentation**, and **submit** application.*

2) Does the research meet the criteria for exempt category 2 (specific procedures)? [45 CFR 46.101 (b) (2)]

Does the research involve only the use of educational tests, survey procedures, interview procedures or observation of public behavior?	☐ Yes X☐ No
Is the information obtained recorded in such a manner that human subjects cannot be identified directly or through identifiers linked to the subjects? (See Appendix B)	X☐ Yes ☐ No

*If **both** questions are answered **yes**, stop here, proceed to **Section I Required Documentation**, and **submit** application.*

3) Does the research meet the criteria for exempt category 3 (public officials)? [45 CFR 46.101 (b) (3)]

Does the research involve only the use of educational tests, survey procedures, interview procedures or observation of public behavior?	☐ Yes X☐ No
Are the human subjects elected or appointed public officials or candidates for public office? **If no, proceed to Category 4.**	☐ Yes X☐ No
Does any federal statute require without exception that the confidentiality of the personally identifiable information will be maintained throughout the research and thereafter? (See Appendix B)	☐ Yes ☐ No

*If **all** questions are answered **yes**, stop here, proceed to **Section I Required Documentation**, and **submit** application.*

4) Does the research meet the criteria for exempt category 4 (existing data/specimens)? [45 CFR 46.101 (b) (4)]

Does the research involve only the collection or study of existing data, documents, records, pathological specimens, or diagnostic specimens?	☐ Yes X☐ No
Will the information be recorded by the investigator in such a manner that the subjects cannot be identified directly or through identifiers linked to the subjects? (See Appendix B)	X☐ Yes ☐ No

*If **both** questions are answered **yes,** stop here, proceed to **Section I Required Documentation**, and **submit** application.*

5) Does the research meet the criteria for exempt category 5 (federal program research)? [45 CFR 46.101 (b) (5)]

Does the research involve studying, evaluating or examining federal public benefit or service programs?	☐ Yes X☐ No
Is the research conducted through a federal agency?	☐ Yes X☐ No

*If **both** questions are answered **yes**, stop here, proceed to **Section I Required Documentation**, and **submit** application.*

6) Does the research meet the criteria for exempt category 6 (taste and food quality)? [45 CFR 46.101 (b) (6)]

Does the research involve a taste and food quality evaluation or consumer acceptance study?	☐ Yes X☐ No
Does the food consumed contain no additives, or a limited amount of food additives at or below a level approved by the FDA or EPA or the Food Safety and Inspection Service of the U.S. Department of Agriculture	☐ Yes X☐ No

*If **both** questions are answered **yes**, stop here, proceed to **Section I Required Documentation**, and **submit** application.*

If no exemptions apply, continue with application.

V. Additional Project Information

1) What human subjects training has the researcher completed (e.g. course work, online certification)? Online training

2) What process is used for obtaining informed consent (attach the informed consent application)? See Appendix for consent application.
Informed consent application

3) Does the research include special populations?

Minors under 18 years of age?	☐ Yes	X☐ No
Persons legally incompetent?	☐ Yes	X☐ No
Prisoners?	☐ Yes	X☐ No
Pregnant women, if affected by research?	☐ Yes	X☐ No

Persons institutionalized?	☐ Yes	X☐ No
Persons mentally incapacitated?	☐ Yes	X☐ No

4) If **YES,** describe additional precautions included in the research procedures.

5) Does the research involve any of the following procedures?

False or misleading information to subjects?	☐ Yes	X☐ No
Withholds information such that their informed consent might be questioned?	☐ Yes	X☐ No
Uses procedures designed to modify the thinking, attitudes, feelings, or other aspects of the behavior of the subjects?	☐ Yes	X☐ No

6) If **YES**, describe the rationale for using procedures, how the human subjects will be protected and what debriefing procedures are used.

7) Does the research involve measurement in any of the following areas?

Sexual behaviors?	☐ Yes	X☐ No
Drug use?	☐ Yes	X☐ No
Illegal conduct?	☐ Yes	X☐ No
Use of alcohol?	☐ Yes	X☐ No

8) If **YES**, describe additional precautions included in the research procedures.

9) Are any portions of the research being conducted online?

Survey posted on a website?	☐ Yes	X☐ No	If yes, assure anonymity
URL for survey includes information that could identify participants?	☐ Yes	X☐ No	If yes, assure anonymity
Invitation to participate sent by email?	☐ Yes	X☐ No	If yes, assure anonymity
Items use drop-down box?	☐ Yes	X☐ No	If yes, assure that items allow choice of "no response"

10) If **YES**, describe additional procedures.

11) Describe the methods used to ensure confidentiality of data obtained.

After enrollment, medical record numbers will only be used to identify patients on documents. Medical record numbers are assigned to all patients at Cancer Treatment Centers of America Midwestern Regional Medical Center. Only the primary researcher will be able to access study related information that is not usually within the patient's medical chart.

Risks and Benefits

1) Describe risks to the subjects and the precautions that will be taken to minimize them. (Risk includes any potential or actual physical risk of discomfort, harassment, invasion of privacy, risk of physical activity, risk to dignity and self-respect, and psychological, emotional or behavioral risk.)

The risks associated with this study protocol include diet intolerance. Subjects who do not tolerate the diet due to an aversion to the foods, or an inability to comply with the diet will return to their normal diet. Subjects may lose weight due to diet intolerance, but weight and diet tolerance will be monitored closely. Weight loss will be addressed by the RD with dietary counseling and recommendations on how to meet caloric needs.

2) Describe the benefits to subjects and/or society. (These will be balanced against risk.)

Possible benefits will include improved response to chemotherapy and increased survival.

Appendix A: Required Elements of Informed Consent

Informed consent is the process of communicating to a prospective participant, in easy-to-understand language (usually sixth- to eighth-grade level), all that he or she needs to know about participating in a research project, and then obtaining the prospective participant's agreement to participate. The following ten elements of consent are widely recognized and, except under certain specific conditions, **must be included in all consent processes and forms**:

1. An explanation of the study, including goals, procedure, and a statement that the study is research.
2. A description of what participants are expected to do and expected length of participation.
3. A description of any likely risks or discomforts for the participants. Potential harm should be explained in language that participants can understand and that relate to everyday life.
4. A description of any likely benefits to the participant or to others.
5. A disclosure of appropriate alternative procedures or courses of treatment, if any, that might be advantageous to the participant.
6. A statement describing the level of privacy assured for collected information (anonymous, confidential) and how private information and information security will be managed.
7. An explanation of whom to contact for answers to questions about the research. When a Mount Mary student is the principal investigator, the name and phone number of a supervising faculty member is required.
8. An explanation of whom to contact for concerns about the participant's privacy and rights, which for Mount Mary University is its IRB Chair.
9. For research involving more than minimal risk, a statement describing any compensation for injuries and contact information. (Minimal risk is a risk of harm to the participant that is no greater than the risk encountered in normal, day-to-day activities or during routine physical or psychological examinations.)
10. A statement that research participation is voluntary and the participant may withdraw from participation at any time, without penalty or loss of benefits to which the participant is otherwise entitled. If the participant is a patient or client receiving medical, psychological, counseling, or other treatment services, there should be a statement that withdrawal from the study will not jeopardize or otherwise affect any treatment or services the participant is currently receiving or may receive in the future. Participants also should be told whether their data will be destroyed should they withdraw from the study. If a survey instrument or interview questions are used and some questions deal with sensitive issues, the participants should be told they may refuse to answer individual questions.

Appendix B: IRB De-Identification Standard for Information

Protecting the privacy of research participants is a general concern in the vast majority of research projects. The degree to which privacy needs to be ensured or maintained depends on the nature of the particular research, its setting, and the research participants. Researchers share a general obligation to design their research to reduce the risks of disclosure of collected information about individual research participants. Thus, the present standard for de-identification of information is useful as a guide to protecting privacy even when it is not required or fully required. In this regard, the researcher should consider the following question when collecting and handling data.

Does the information I am accessing, recording, and/or disclosing contain identifiers? Simple access to information may be without concern, for example when the researcher is an employee who routinely handles the records in carrying out his or her position. But, the presence of identifiers in any **recorded or disclosed** information in the research means the information is not anonymous and so does not meet the IRB de-identification standard, which in some cases may also disqualify the research from exemption from IRB review. The IRB de-identification standard includes all 18 direct identifiers specified in the HIPAA Privacy Rule de-identification standard—*45 CFR 164.514(b)*. Below are listed specific direct and indirect identifiers that lead to information not being anonymous.

Identifiers: Direct; Indirect

One way to distinguish between information that is truly anonymous and information that is simply being kept confidential is to determine whether the data set contains direct or indirect identifiers. Information in a data set with either direct or indirect identifiers is not anonymous.

Direct Identifiers include:

- Names
- Addresses
- Telephone and fax numbers
- Email addresses, IP addresses, and URLs
- Social Security numbers
- Medical record numbers
- Account numbers, such as those associated with bank accounts or health plans
- License or certificate numbers, including driver's license numbers
- License plate numbers and other vehicle identifiers
- Fingerprints, voiceprints, or full-face photographic images
- Other unique characteristics or identification numbers (example student ID numbers)

Indirect Identifiers can be combined with publicly available information to identify individuals. The determination of indirect identifiers depends on the nature of the research participants. For example, in a study of residents of the state of Wisconsin, the information that someone graduated from one of the UW system schools probably would not be a unique identifier. However, in a study of small business leaders in Racine, WI, the same information might well

apply to only one individual. In general, if any single variable in a data set applies to fewer than five participants, it is considered a potential indirect identifier.

Examples of indirect identifiers include:

- Detailed geographical information, such as state, county, or census tract of residence
- Organizations to which participants belong
- Educational institutions from which participants graduated
- Exact occupations
- Places where participants grew up
- Many dates, e.g. birth dates, hospital admission dates, high school or University graduation dates, etc.
- Detailed income information
- Offices or posts held by participants.

Appendix B

Consent Form for Participation in a Research Study

Mount Mary University

A Randomized Cross-Over Trial Assessing the Impact of a Gluten Free Diet Compared to Control on Crohn's Disease Activity, Inflammation, and Symptoms

Description of the research and your participation

You are invited to participate in a research study conducted by Danielle Hill. The purpose of this research is to determine if a Ketogenic diet impacts response to first line systemic therapy for stage IV colon cancer, body composition, various serum markers, and quality of life.

Your participation, depending on assigned study group, will require you to follow a 12 week diet intervention or continue your typical diet pattern. During this intervention, you and your caregivers will be responsible for all meal prep. If you have been randomized to the intervention group, you will be provided one hour of diet education from a registered dietitian on the Ketogenic diet. Within this consult, you will be educated on how to assess urinary ketones at home properly. Individuals randomized to the control group will be provided education from a registered dietitian on general evidence based cancer related recommendations. The intervention group will be required to follow up with a dietitian every two weeks. At these visits biomarkers, complete metabolic panel, complete blood count, and serum ketones, will be assessed. Blood collected at baseline and week 12 will also assess a lipid panel and hemoglobin A1c. The control group will have the option to follow up as needed. In the intervention group, uou will be evaluated by a gastroenterologist at baseline and undergo a routine colonoscopy with biopsies.

Risks and discomforts

There are no known risks associated with this research aside from the risks you accept when being consented for chemotherapy.

Potential benefits

Currently, there are no known benefits to you that would result from your participation in this research. This research may help us to understand the role a Ketogenic diet may play in cancer activity and the body's response to conventional systemic therapy.

Protection of confidentiality

Every effort will be made to maintain the confidentiality of your participation in this project. Confidentiality will be maintained within legal limits. Your identity will not be revealed in any publication resulting from this study.

Voluntary participation

Your participation in this research study is voluntary. You may choose not to participate and you may withdraw your consent to participate at any time. You will not be penalized in any way should you decide not to participate or to withdraw from this study.

Contact information

If you have any questions or concerns about this study or if any problems arise, please contact Danielle Hill of Mount Mary University at 847.308.6533. If you have any questions or concerns about your rights as a research participant, please contact the Mount Mary University Institutional Review Board at 414.258.4810.

Consent

I have read this consent form and have been given the opportunity to ask questions. I give my consent to participate in this study.

Participant's signature_____ Date:_____

A copy of this consent form should be given to you.