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Using the Ketogenic Diet as an Adjuvant to Cancer Therapy: A Systematic Review

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USING THE KETOGENIC DIET AS AN ADJUVANT TO CANCER THERAPY: A SYSTEMATIC REVIEW

by

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ABSTRACT

Cancer is the second leading cause of death in the United States. Evidence shows that a conventional western diet may contribute to the proliferation of cancer cells, affecting their prognosis. The aim of this review is to examine the efficacy and safety of using the ketogenic diet as an adjuvant to traditional cancer therapy. The systematic literature search was performed in October 2018 on two search engines: EBSCOhost (Medline, CINHAL, Cochrane Central Register of Controlled Trials) and Web of Science using the following key terms: ketogenic diet, high fat & low-carbohydrate diet, Atkins diet, cancer or neoplasms+. The search limitations included clinical studies among adult cancer patients. A total of 544 publications were initially identified. After the first title/abstract screening, 22 articles were eligible for full-text screening; finally, 3 were eligible for data extraction. We synthesized the effects of the ketogenic diet on cancer progression and safety by extracting and summarizing data on 4 items: 1) study characteristics, 2) characteristics of study participants, 3) diet composition and duration, and 4) key findings for efficacy and safety. Although only 3 studies were included, it was observed that more patients who adhered to the ketogenic diet than patients who did not experienced stability of disease and response to treatment. Patients who received the ketogenic diet also experienced a decrease in tumor size, cholesterol, fasting glucose, and triglyceride levels at 90 days. No statistically significant anthropometric changes were experienced; patients weight was maintained. However, more clinical evidence is necessary before applying the ketogenic diet in an oncological setting.

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Chapter I. Introduction

Chronic diseases are the leading cause of death among Americans. Cancer is the second leading cause of death under heart disease. Although the lifespan is significantly longer than it was in the 20th century, the last 10-20 years of life are made up of poor health and quality of life (Fries, 2003). According to Fries' Theory, the lifespan may remain the same, but the onset of chronic diseases may occur much later in life due to improvement of disease management and treatment (Fries, 2003); therefore, chronic diseases are inevitable, and more effective treatment is necessary.

For years, various types of cancer therapies have been discovered and explored through clinical trials. In 1940, the United States (U.S.) Army discovered mustard gas, which was found to be toxic for osteoblasts. A compound called nitrogen mustard was utilized to kill cancer cells by damaging their DNA; it was used to fight lymphoma. Later, a compound related to folic acid called aminopterin was used to treat children with leukemia and led them into remission. Aminopterin was replaced with methotrexate--a cancer treatment drug commonly used today (American Cancer Society, 2014); this began the evolution of chemotherapy.

Although chemotherapy treats cancer by killing cancer cells, it also has shown lower efficacy for cancers with more severe prognosis (Torre et al., 2015). There were an estimated 158,000 deaths among 224,390 cases of lung cancer diagnosed, as well as 40,500 deaths among 49,000 cases of pancreatic cancer diagnosed (Torre et al., 2015); moreover, a compliment to traditional therapy may be beneficial and necessary for aggressive cancers (Fine et al., 2012). Evidence has shown that diets rich in omega-3 fatty acids and phytochemicals allow for treatment efficacy among other advantages (Cancarini et al., 2015). In addition, fasting has also been observed to

improve chemotherapy outcomes for patients who fasted a couple days before beginning treatment (Fine et al., 2012).

However, it is important to review the safety of a carbohydrate-restricting diet as an adjuvant to cancer therapy, considering the large consensus in literature regarding weight maintenance and muscle mass of patients during cancer treatment (Bozzetti & Zupec-Kania, 2016). Patients with advanced diseases may experience cachexia, which is defined as reduced body weight and wasting due to tumor growth and cancer treatment's adverse effects such as anorexia. Twenty percent of cancer deaths have been considered in association with cachectic patients (Terranova et al., 2018). Patient condition is largely dependent on cancer cell proliferation rates and vice versa (Terranova et al., 2018); it is important to acknowledge this issue while studying nutritional approaches.

Cancer cells proliferate by anaerobic glycolysis; in other words, cancer thrives on sugar to grow and spread throughout the body. The ketogenic diet suggests a diet rich in fat (90%) and restrictive of carbohydrates (2%). During the ketogenic diet, blood sugar levels are decreased drastically, which forces fat to become the main source of energy for the cells through oxidative phosphorylation; this creates what is referred to as a ketogenic state or ketosis (Skinner, Trujillo, Ma, & Beierle, 2009). Additionally, some key differences when comparing healthy cells to cancer cells are inefficiencies in the cancer cell mitochondria, which require the increase in glucose to make up for the excess peroxidation; hence, the hypothesis in respect to dependence on oxidation of fatty acids by oxidative stress within tumor cells was postulated (Zahra et al., 2017). Evidence has pointed to a significant reduction in tumor growth, and in fact has shown a lack of glycolytic activity to result in

disruption of cancer cell proliferation (Blaylock, 2013). Overall, using the ketogenic diet to enhance cancer therapy outcomes is an important topic to consider in order to benefit patients with advanced diseases.

Chapter II. Objectives and Hypotheses

The aim of this study was to examine the efficacy and safety of using a ketogenic diet as an adjuvant to traditional cancer therapies by synthesizing data from previous clinical trials; these studies were reviewed regarding the mechanisms of normal cells versus cancer cells and their function in relationship to the ketogenic diet. This study may potentially propose the ketogenic diet as a complementary treatment for advanced patients with cancer receiving traditional therapies; therefore, reducing the adverse effects of these traditional cancer therapies if ketogenic diet shows its safety among patients with cancer.

Hypothesis 1: The ketogenic diet as an adjuvant therapy would enhance cancer therapy and reduction in cancer progression, measured by compliance to cancer treatments and/or biomarkers for cancer cell metabolism (i.e. TKTL1, IGF-1, oxidative stress, blood glucose, blood ketone level).

Hypothesis 2: The ketogenic diet as an adjuvant therapy would be safe and compliable for patients undergoing cancer therapy, measured by adverse effects (i.e. nausea, cachexia, vomiting, fatigue, hunger, etc.) and/or adherence to the ketogenic diet.

Chapter III. Literature Review

Cancer Statistics and Therapy

Cancer is the second leading cause of death in the United States, next to heart disease; one in two people will have cancer during their lifetime, and one in four people will die from cancer (DiPietro, 2019). In 2017, 1,688,780 new cancer cases were reported, with 600,920 deaths in the United States alone (DiPietro, 2019). According to the World Health Organization, 9.6 million people were estimated to die of cancer in 2018. In 2010, the nation's financial cancer burden was an estimated 1.16 trillion dollars (World Health Organization, 2018). The four most common and aggressive cancer sites include colon and rectum, lung and bronchus, breast (women), and prostate (men) (DiPietro, 2019). According to the Centers for Disease Control and Prevention, the top ten most common cancer cases, from greatest to least, are female breast, prostate, lung and bronchus, colon and rectum, corpus and uterus, melanomas of the skin, urinary bladder, non-Hodgkin's lymphoma, kidney and renal pelvis, and thyroid (2018). By rates of death, the top ten most common cancer cases from greatest to least include lung and bronchus, female breast, prostate, colon and rectum, pancreas, ovary, liver and intrahepatic bile duct, leukemias, non-Hodgkin's lymphoma, and corpus and uterus (Centers for Disease Control and Prevention, 2018). It is notable that the top three common cancers, high in both incidence rate and mortality rate, are lung and bronchus, female breast or male prostate, and colon and rectum; these common cancers clearly need improvements in treatment approach, which may include supplementing traditional therapy.

Along with other noncommunicable diseases, cancer has long been a major focus in research. Many methods of treatment have been applied over the years, such as chemotherapy, radiotherapy, hormone therapy, etc. Cancers that are harder to detect have shown high rates of mortality (DiPietro, 2019). Cancers of the pancreas, liver, gallbladder, lung, esophagus, ovary, and brain have a five-year survival rate of less than fifty percent due to late detection and need for advanced treatment (DiPietro, 2019). Thus, adjuvant therapy to supplement conventional cancer therapies to patients with advanced cancer stages is becoming urgent and necessary. Appendix Table A1 shows incidence and mortality of most common cancers, and pancreatic and lung cancers need more research to improve their prognosis.

Cancer and Nutrition

Nutrition plays a paramount role in cancer, particularly in incidence rates and treatment outcomes. Antioxidant micronutrients are important for higher efficacy of cancer therapies (Grober, Holzhauer, Kisters, Holick, & Adamietz, 2016). Majority (30%-90%) of patients with cancer are malnourished and are recognized by a cachectic phenotype (Grober et al., 2016). Cachexia is a severe condition seen in patients with cancer, in which lean body mass and adipose tissue begin to waste away; this is one of chemotherapy's many adverse effects. Cachexia is a result of not only the tumor cell's consumption of energy, but of the tumor cell's pro-inflammatory properties such as cytokines, catabolic proteins, and catabolic hormones that deteriorate metabolic homeostasis (Grober et al., 2016). Cachexia is specifically evident within cancers of higher mortality and aggressive prognosis such as

pancreatic, bronchial, and gastric (Grober et al., 2016). Statistically, the mortality rate in malnourished patients with cancer is higher by about 30%, and up to 50% of patients suffer from cachexia, resulting in rapid weight loss, fatigue, low quality of life, and reduced survival time (Grober et al., 2016). As seen in Table A2 of the Appendix, the 5-year survival rates are not good for majority of cancer types. A nutritional adjuvant therapy may be proposed to reduce the adverse effects of traditional therapies.

Micronutrient deficiencies have been found to impact markers of oxidative stress in factors such as cytoreductive measures, risk of complications, impaired immunocompetence, delayed wound healing, fatigue, and depression (Grober et al., 2016). Macronutrients are the carriers of micronutrients; these include fats, proteins, and carbohydrates. Inadequate intake of macronutrients leads to inadequate intake of micronutrients, resulting in malnutrition. In addition, the adverse effects of chemotherapy and radiotherapy such as vomiting, diarrhea, changes in taste, aversion of foods, appetite loss and inflammation responses, increase the necessary requirement of micronutrient consumption during cancer treatments in order to lessen or eliminate these effects. (Grober et al., 2016). As seen in Table A3 of the Appendix, incidence of malnutrition is evident in cancers with poor prognosis. Hence, there is the necessity of nutritional therapy as an adjuvant to oncological treatment.

Additionally, there is a major difference in nutritional needs in order for both healthy and cancer cells to proliferate. Since cancer cells contain inefficiencies in their mitochondria, they require an increase in glucose to make up for the excess hydrogen peroxide; hence, we can hypothesize that tumor cells depend on oxidation of fatty acids by oxidative stress (Zahra et al., 2017). External peroxide radicals are formed from pharmacologic ascorbate, which are meant to

deplete adenine triphosphate to cancer cells by mediating toxicity (Grober et al., 2016). According to the Warburg effect, cancer cells depend on anaerobic metabolism for ATP generation; therefore, loss of glucose in the diet may result in decreased ATP production, and in turn lead to cancer cell death (Grober et al., 2016). Cancer cells cannot rely on ketone bodies for energy. Evidence has pointed the ketogenic diet to a significant reduction in tumor growth, and in fact has shown a lack of glucose utilization, which results in cancer cell disruption (Blaylock, 2013). Overall, using the ketogenic diet is promising to enhance cancer therapy outcomes to benefit patients with advanced diseases.

The Ketogenic Diet

Numerous preclinical studies have indicated evidence of the ketogenic diet as therapeutic potential for patients with cancer (Tan-Shalaby et al., 2016). Originally, the ketogenic diet was used as a diet regimen for epilepsy in children and has been a successful treatment for over 80 years (Hae-Yun et al., 2017). According to Masood and Uppaluri, various studies have shown promising results using the ketogenic diet as an intervention for various neurological disorders, including dementia, amyotrophic lateral sclerosis, traumatic brain injury, metabolic disorders, acne, epilepsy, and cancer (Masood & Uppaluri, 2018).

The ketogenic diet differs greatly from the conventional diet of western society. Ketogenic diet typically consists of 90% fat, 8% protein, and 2% carbohydrate (Allen et al., 2013). Fat becomes the primary macronutrient of interest in order to create a metabolic state that mimics fasting (Tan-Shalaby et al., 2016). The ketogenic diet induces a decrease in blood glucose and an increase in blood ketone bodies, which is a metabolic state referred to

as *ketosis*. Rather than cells relying on glycolysis for energy, they rely on fat oxidation and mitochondrial respiration. By enhancing oxidative stress, the ketogenic diet is believed to enhance the effects of traditional cancer therapies such as chemotherapy and radiotherapy (Allen et al., 2013).

The Atkins diet has very similar characteristics to the ketogenic diet; they are both low carbohydrate and high fat diets. The Atkins diet may include a diet as low as 20 grams of carbohydrates a day; thus, it also induces a state of ketosis and may be maintained for around the same duration as the ketogenic diet (Gardner, Kiazand, Alhassan, & et al., 2007). Although modified Atkins diet and ketogenic diet are commonly interchangeable terms, the Atkins diet differs in regard to protein composition. Unlike the ketogenic diet where protein should only be up to 20% of the daily caloric intake, the Atkins diet has no cap on protein intake. In a process known as gluconeogenesis, the body leaves ketosis and begins to break down protein into glucose because of low carbohydrate levels; this is why protein in the ketogenic diet must be in moderation (Kaleta et al., 2011).

Dr. Atkins created the Atkins diet to address the obesity epidemic; he believed that this epidemic was due to the high consumption of refined carbohydrates. Atkins is typically used to treat patients with diabetes, in order to reduce blood glucose and insulin levels. The ketogenic diet similarly reduces blood glucose and insulin levels, resulting in improved body weight, serum profiles, anthropometric markers, and reduction in tumor progression (Hae-Yun et al., 2017). Blood ketone levels and blood glucose levels may be the key factors which can mediate cancer progression through the ketogenic diet.

Indicators for Cancer Progression

A hallmark feature of metastatic neoplasms is lactate production in the presence of oxygen, also known as aerobic fermentation (Tan-Shalaby et al., 2016). Due to the lack of function or structure of the mitochondria in cancer cells, aerobic fermentation is a compensatory response to the deficiency of oxidative phosphorylation. As a result, tumor cells thrive on glucose for growth and survival (Tan-Shalaby et al., 2016). In order to inhibit tumor proliferation, blood glucose must be reduced, and blood ketone bodies must be increased. Ketone bodies then utilize the functional mitochondria in a healthy cell for energy while cancer cells starve. Therefore, the ketogenic diet prevents tumor cell proliferation by increasing oxidative stress to cancer cells while normal cells can thrive on ketones even when glucose is scarce (Tan-Shalaby et al., 2016).

In addition to decreased tumor size by means of lowering blood glucose, other biomarkers play an important role in cancer cell apoptosis. Insulin is a crucial hormone in anabolic processes and glucose homeostasis (Boyd, 2003). Elevated insulin levels or insulin-like growth factor (IGF)-1 in the blood affect cancer prognosis due to interference with cancer therapy (Boyd, 2003). A novel biomarker for tumor progression is transketolase-like 1 (TKTL1), which is a protein coding gene as well as a blood glucose regulator; in high levels it will worsen disease prognosis (Hae-Yun et al., 2017). Another indicator of cancer cell progression may be host's weight loss due to tumor proliferation.

Safety

Various metabolic markers such as triglyceride will be important to note while using the ketogenic diet as a nutritional compliment to cancer therapy due to high fat content.

Method of Systematic Review

A systematic review is a type of literature review that answers a defined research question that uses systematic and reproducible methods to identify, select, and critically appraise all relevant research, and synthesize studies (Uman, 2011). The stages of a systematic review are summarized below:

1) Formulate the review question.

A question is necessary while forming hypotheses to begin this study.

2) Define inclusion and exclusion criteria.

Prior to beginning the review, all the study components must be considered; this may indicate study criteria such as age, disease type, intervention and control type, and outcome variables.

3) Develop search strategy and find studies.

A list of key terms may be used to run electronic searches in finding studies relevant to the topic of choice. The goal will be to balance search sensitivity in order to obtain a large amount of studies, as well as a minimal amount of irrelevant studies.

4) Sort and select studies.

Studies may be selected according to inclusion and exclusionary criteria to be reviewed. This process involves reviewing titles and abstracts and sorting, which is recommended to be done by at least two reviewers. Inter-rater reliability is established to ensure that the studies represent the variables hypothesized.

5) Extract data.

Information may be organized through tables as a helpful method to extract data. Inter-rater reliability is established again to ensure data entry errors are avoided.

6) Assess study quality.

Follow recommended guidelines and standards of each randomized control trial to include in the review.

7) Analyze and interpret results.

The interventions of highest efficacy and the conditions under which they were used will be summarized as well as the topics and interventions that may require further study.

8) Disseminate findings.

Find the target audience in which the research findings will pertain to and summarize findings as such. The review will create a means of decision-making pathways.

Chapter IV. Materials and Methods

Study Design

A systematic review was conducted to investigate the efficacy and safety of ketogenic diets as adjuvant to cancer treatment in patients with cancer synthesizing the available results from clinical trials.

Review Questions

1. What is the efficacy of ketogenic diet in cancer treatment?
2. Is ketogenic diet safe among patients with cancer?

Searches

CINAHL, MEDLINE (Pubmed), Cochrane, PhychINFO and Web of Science were searched for studies investigating the efficacy and/or safety of the ketogenic diet among adult patients with cancer when they are undergoing traditional cancer therapy from conception to November 1, 2018. Key search term included ketogenic diet, high fat & low-carbohydrate diet, Atkins diet, cancer or neoplasms+. In addition, the reference lists of the included studies and relevant reviews will be also searched to identify additional publications.

No restriction was applied on the area/location where the studies were conducted, but the searching was limited to the following: studies published in the English language, studies conducted among human adults, and studies employed clinical trials with a comparison group.

Types of studies included

Only clinical trials were included. Studies were excluded if they were: (1) other publication types (such as protocols, reviews, observational studies-cohort studies, case-control studies, or cross-sectional studies), or not peer-reviewed publications (such as conference abstracts, editorial, commentary), (2) there was no comparison group, and (3) duplicate publications.

Condition or domain being studied

This review aimed to examine the efficacy and safety of the ketogenic diet among patients with cancer. In this review, we focused on the efficacy and safety of the ketogenic diet as an adjuvant therapy during active cancer treatment. Efficacy was measured by cancer proliferation (using MRS scanner), tumor size or metabolic markers (amount of ketone bodies in brain or urine), reduction in adverse responses and compliance to the traditional cancer therapies when the ketogenic diet is prescribed compared to when the standard diet is consumed. Safety was measured by patient compliance to the ketogenic diet itself and/or any self-reported adverse responses to the diet (anthropometric measures, nausea, vomiting, diarrhea, fatigue, etc.).

In this study, the ketogenic diet was defined as a very high fat, low protein, and very low carbohydrate diet composition. The fat composition needs to range from 80 to 90% of a 2,000-calorie diet, which calculates to around 180 to 200 grams per day; protein needs to be around 8% to 10% of a 2,000-calorie diet, which is 40 to 50 grams per day; carbohydrate needs to be between 2 and 5% of a 2,000-calorie diet, or 10 to 25 grams per day (Allen et al.,

2013). The modified Atkins diet was also included in this review regarding the reduction of blood glucose and insulin levels and the increase of blood ketones.

Participants/population

Participants targeted in our review are adult (aged ≥ 18 years old), cancer survivors (regardless of the cancer type and survivorship duration). The term "cancer survivors" refers to all people who are living with a diagnosis of cancer, and those who have recovered from the disease; given this definition, cancer survivorship begins at the time of diagnosis.

Intervention(s), exposure(s)

Ketogenic diet and/or Atkins diet

Comparator(s)/control

Conventional diet (no restricted diet)

Primary outcome(s)

Efficacy and/or safety of ketogenic diet

Data extraction (selection and coding)

Data extraction was performed using an extraction form in a systematic review software, DistillerSR. Four major pieces of information were extracted from each article and organized into a table:

1) The study characteristics: title, first author, publication year, study type, sample size (for each arm), and where the study was conducted (Table 1).

2) The participants (cancer survivors) characteristics: cancer type (specific or all types), cancer stage, time since cancer diagnosis, cancer treatments received, current cancer treatment, patient age (median and range), and gender composition.

3) The diet: macronutrient composition of the diet regimen (treatment vs. control group), duration of diet, and follow-up period.

4) Key findings: efficacy biomarkers for cancer progression included in the study to measure efficacy. Safety was measured by occurrence of adverse responses to the diet in addition to the compliance to diet.

Strategy for data synthesis

Due to the only 3 studies satisfied the eligibility criteria, no meta-analysis was performed, and a qualitative review of three clinical trials was performed.

Analysis of subgroups or subsets

The number of identified studies did not allow subgroup analysis to be carried out.

Chapter V. Results

Search Results

A total of 544 articles were identified through database searching. Zero studies were found through additional sources. After two duplicates were removed, 534 records were screened, and 512 were excluded during title screening due to lack of relevance, the ketogenic diet not being provided during treatment, the study types that were not clinical trials and the study sample not being patients with cancer. Subsequently, 22 articles were reviewed for full-text eligibility; from these, three clinical trials were included (Figure 1).

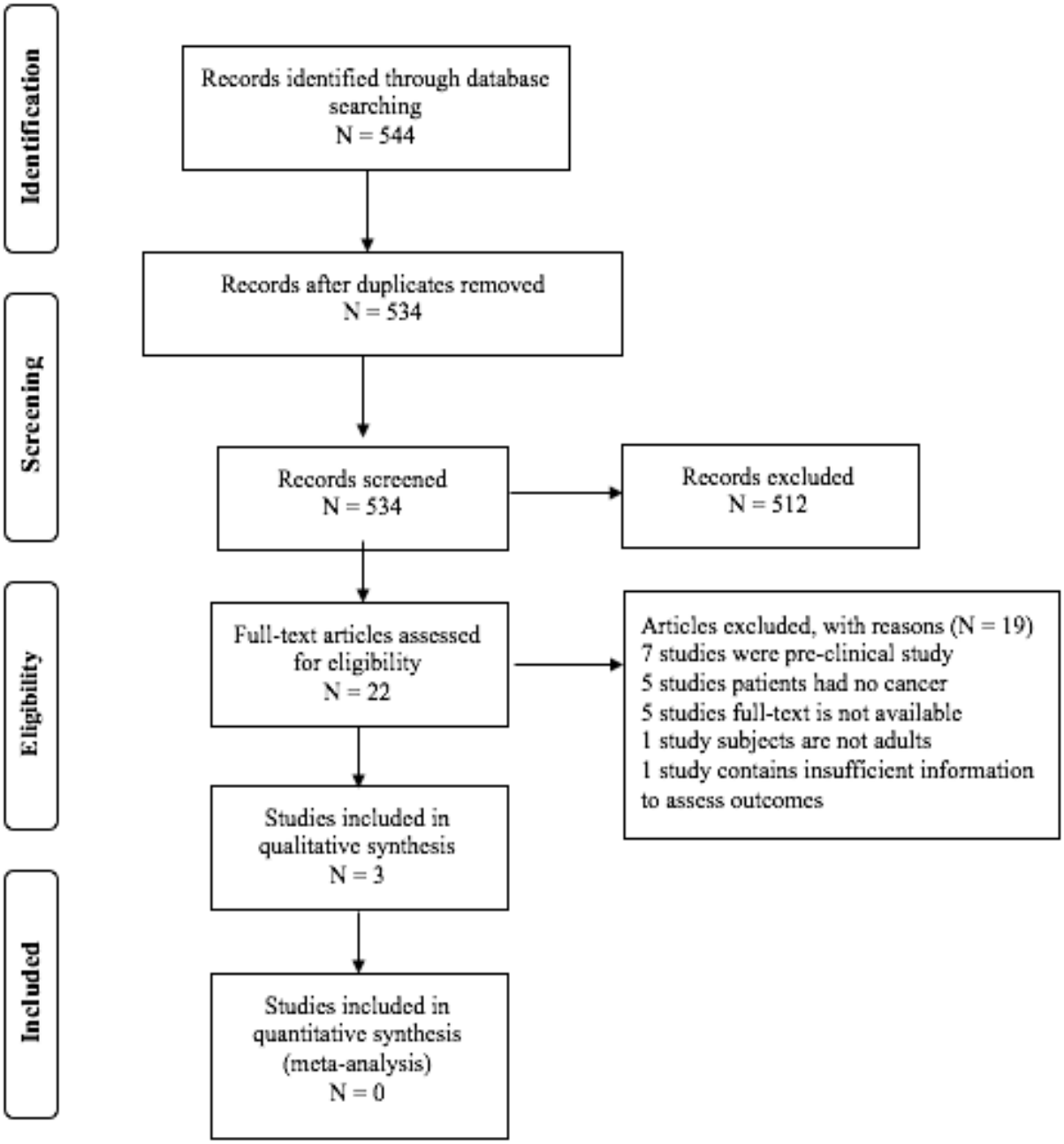

Figure 1. PRISMA flow chart

Characteristics of Included Studies

Three control trials were included for data extraction. There were 47 participants altogether, with 32 cases and 15 controls. The age range was between 27 and 69 years, and among all three studies, the cancer site was of the brain. Two studies had recurrent cancer while receiving chemotherapy, radiotherapy, and surgery. One study had mixed stages while receiving chemotherapy. The cases received the diet intervention during the concurrent cancer therapies. One of the studies administered the diet for 8 weeks, while the other two studies administered the diet for twelve. The classic ketogenic diet with a 4:1 ratio of fats to carbohydrates, had 4/5 (80%) patient compliance throughout the 8-week intervention period (Artzi et al., 2017). The modified Atkins diet/low glycemic index diet which include 60%-70% fat and 23%-30% protein (Martin-McGill, Marson, Tudur Smith, & Jenkinson, 2018), had lower compliance overall (50%-67%) during the 12-week period (Santos et al., 2018).

The Effect on Compliance to Cancer Treatment

The primary outcomes of the study included efficacy of the ketogenic diet to enhance therapies for the patients who underwent the dietary intervention. The patient who was able to adhere to the ketogenic diet was observed to have ketone bodies in their brain using an MRS (Magnetic Resonance Spectroscopy) scanner (Artzi et al., 2017); this patient experienced stable disease because they kept the diet very strictly. Although this patient had experienced stable disease, the ketogenic diet was not used conjunctively to other therapies. The patients who complied to the diet intermittently happened to be the ones also receiving other forms of therapy,

such as chemotherapy, surgery, and radiation (Artzi et al., 2017). Further study is required to differentiate between the impact of the chemotherapy/radiotherapy and the diet itself.

The Effect on Cancer Progression and Metabolic Biomarkers

In one of the studies, the comparative arms revealed a clear response to the diet through therapy outcomes (Santos et al., 2018). Partial response was recorded for 77.8%, stable disease was recorded for 11.1%, and progressive disease recorded for 11.1% of those who maintained dietary compliance (Santos et al., 2018). Within the standard diet group, partial response was only seen in 25%, stable disease was 25%, and 50% experienced disease progression (Santos et al., 2018). Although the cases and control outcomes were not statistically significant, there was a clear trend in tumor reduction size. The effect of the ketogenic diet paired with cancer therapy is shown for a recurrent glioma patient over a period of 3 months. The MRI scans have shown a notable reduction of tumor size after treatment (Santos et al., 2018). In addition, no adverse effects were reported for the intervention group.

The Safety of the Ketogenic Diet

According to the Martin-McGill study, the efficacy of the diet was not measured due to limited resources, but the diet was reported safe for patients (Martin-McGill et al., 2018). Mild constipation was the only adverse response reported for two of the patients, which was fixed shortly after by increasing fibrous foods such as flax and oral fluids (Martin-McGill et al., 2018). In addition, the Santos study reported that 0/17 patients experienced adverse effects of the diet

and minimal weight changes (Santos et al., 2018). One patient who received the intervention did not comply due to an unrelated chest infection, and another patient did not comply due to dietary preference (Martin-McGill et al., 2018). Out of the 28 patients who received the diet included in this review, 17 of them complied (61%). No adverse responses were observed for the patients who received the ketogenic diet.

Anthropometric parameters and nutritional statuses were measured in two of three studies at baseline and after the duration of the diet. For instance, cholesterol has been one of the concerns of the diet due to its high lipid content. In the study according to Santos, the total cholesterol of the treatment group was significantly lower by the end of the 90-day trial than the control group (Santos et al., 2018); this was said to be due to the larger amount of monounsaturated fats/polyunsaturated fats, rather than saturated fats. Furthermore, low-density-lipoprotein and triglyceride levels had a statistically significant decrease following the ketogenic intervention (Santos et al., 2018). Although not statistically significant, there was a moderate decrease in fasting glucose levels in the intervention group. It was mentioned that this may have been due to the diet duration of 90 days (Santos et al., 2018).

McGill's study reported that there were no statistically significant changes in anthropometric measures assessed at baseline compared to the end of the 12 week intervention; these measures included weight, height, liver function, and fasting lipid and glucose levels (Martin-McGill et al., 2018). The ketogenic diet had either minimal or positive effects for patients' anthropometric and nutritional statuses.

Table 1. Study Characteristics

Author	# Sample (treatment-control), male (%)	Age: median (range)	Cancer Site	Treatment	Ketogenic Diet
Artzi, 2017	9 (4-5), 66.7%	42 (27-69)	Brain Cancer (GBM), Mixed stages	Chemotherapy	Classic Ketogenic Diet 4:1 (Fat 90%) 8 weeks
Martin-McGill, 2018	6 (6-0), 100%	46(34-66)	Brain Cancer (GBM), Mixed stages	Chemotherapy, Radiotherapy, Surgery	Low Glycemic Index Diet (Fat 60-70%, Protein 23-30%) 12 weeks
Santos, 2018	32 (17-15), 59.1%	53 and 48(27-55)	Brain Cancer (GBM), Recurrent	Chemotherapy, Radiotherapy, Surgery	Modified Atkins Diet (Fat 60-65%, Protein 30%) 12 weeks

GBM: Glioblastoma Multiforme

Table 2. Study Outcomes

Author	Efficacy	Safety
Artzi, 2017	• SD or PR: 3/5 (60%), PD: inconclusive • SD: 1/5 (20%) diet alone • High level of ketone bodies in brain	• N/A • 4/5 (80%) complied
Martin-McGill, 2018	• NA	• 2 mild constipation • No changes in anthropometry or laboratory values • 1 unrelated chest infection • 4/6 (67%) complied • 1 clinical deterioration • 1 dietary preference
Santos, 2018	• SD: 1/9 (11%) vs. 2/8 (25%) • PR: 7/9 (78%) vs. 2/8 (25%) • PD: 1/9 (11%) vs. 4/8 (50%)	• 0/17 adverse effects • 9/17 (52%) complied • 90 days: Lower total cholesterol, LDL-C, triglyceride levels, moderate decrease fasting glucose

SD: stable disease, PR: partial response, PD: progressive disease, NA: no answer

Chapter VI. Discussion

Three studies pertaining to patients with malignant gliomas were included in this review; this pattern of the cancer site may be due to the accumulation of evidence for the use of the ketogenic diet for neurological disorders such as epilepsy, the aggressive phenotype of brain malignancies, and the lack effective treatments in this particular cranial region. The prognosis for intracranial malignancies is poor (Martin-McGill et al., 2018). The current standard of care for patients with glioma consists of chemotherapy, radiotherapy, and surgery when feasible. According to Stupp et al., the vast majority (89-97%) of patients succumb to brain cancer within five years of diagnosis (Stupp et al., 2009). Although patients initially respond well to the standard treatment regimen, the effectiveness wanes over time due to the tumor's drug resistance (Stupp et al., 2009). The standard of care currently being used (chemotherapy, radiotherapy, and surgery) is necessary, but may be paired with the ketogenic diet to improve prognosis. In this review, the ketogenic diet paired with standard cancer therapies has shown to improve disease outcomes and to be safe.

The most common types of brain tumors in adults are stage III astrocytoma and stage IV glioblastoma, while the most common type of tumor seen in pediatric patients is medulloblastoma (Chen, da Fonseca, & Schönthal, 2018). Other primary tumor types are benign but can quickly progress into an aggressive phenotype. Secondary tumors, that come from systemic cancers are largely prevalent, with around 200,000 new diagnoses in the United States each year (Stupp et al., 2009). Either primary or secondary, tumors of the brain have an aggressive phenotype.

It is clear that more effective cancer treatments are needed, especially for glioma malignancies (Santos et al., 2018); this is due to the blood-brain barrier (Chen et al., 2018). The blood brain barrier blocks off systemic circulation to the brain; therefore, treatment is not usually efficacious for brain tumors (Chen et al., 2018). A novel cancer therapy has been the only therapy in history to be delivered intranasally; this potent therapy is naturally occurring compound found in plants such as citrus fruits and lavender, called perillyl alcohol. When it was first developed and studied clinically, it was given orally and was intolerable for the gastrointestinal tract (Stupp et al., 2009). The therapy has had very promising effects when delivered intranasally (Chen et al., 2018). Yet, even with potent cancer therapies, the prognosis for this cancer has not improved significantly; therefore, it has been paired with the ketogenic diet for treatment enhancement (Artzi et al., 2017).

One of the shared realities of the three studies included in this review is lack of knowledge of what the ketone bodies in the brain actually indicate. The ketone bodies showed no specific pattern to patients or time points. When the ketone bodies were of high concentration, a conclusion could not be drawn on whether the ketones were high due to increased utilization or production (Artzi et al., 2017). Also, studies that have used urine ketone measures at a lower cost do not assess results relevant to the cerebral ketone levels. Additionally, there are no clear results as to why ketosis helps with seizure control, although there has been evidence of it since the diet was introduced for children with epilepsy over 80 years ago (Artzi et al., 2017). Brain scans were also utilized while treating children with epilepsy, in the same way that they were used in the Artzi's study to assess ketone accumulation. In all three studies, glioma was compared to past

studies when the diet was applied to pediatric epilepsy in regard to measurement, efficacy, and safety. However, there is a need for more clinical evidence in an oncological setting.

Gliomas usually lead to seizures due to the cranial pressure from tumor progression (Santos et al., 2018). It has been found that anti-epileptic drugs may interfere with cancer therapy outcomes; therefore, the ketogenic diet may be crucial to alleviate the need for them, as well as maintain the integrity of the cancer treatments (Bruna, Miró, & Velasco, 2013); this evident relationship may be the reason the ketogenic diet has been tested firstly for glioma patients.

Although there have been many human clinical studies for using the ketogenic diet for epilepsy, using the ketogenic diet as a metabolic therapy for cancer is a very recent emergence. Most studies have been done on rat models, providing evidence that the diet is safe and feasible during traditional therapies. There have been very few human studies, only including case studies which do not have a control group. Until there are more human clinical trials, the use of the ketogenic diet as a metabolic therapy for patients with cancer will not be introduced.

The studies included in this review had inconsistent ways of measuring the safety and efficacy of the ketogenic diet combined with cancer treatment. For instance, Artzi's study did not measure safety, and McGill's study did not measure efficacy. Santos measured both safety and efficacy, but the markers used to measure the patients at baseline and after the intervention were inconsistent among the other studies. In addition, McGill's study lacked a control group, which did not allow a clear comparison to a conventional diet paired with cancer therapies (Martin-McGill et al., 2018). Among the

three studies, the macronutrient composition for the ketogenic diet among the intervention group varied, which may have impacted the level of compliance or efficacy altogether. The inconsistencies of measurement tools did not allow for an opportunity to draw solid conclusions. The quality of the studies was not assessed due to the limited information available; therefore, reliability of the results is lacking. Statistical analysis was not possible among only three included studies; hence, qualitative synthesis was performed rather than quantitative meta-analysis.

Chapter VII. Conclusion

There is plenty of evidence from rat clinical studies of lesion reduction. There is evidence of the ketogenic diet in relation to the metabolic pathway of epilepsy and seizure reduction. The ketogenic diet does not result in any severe adverse outcomes. However, further high-quality human clinical trials need to be performed concerning the use of the ketogenic diet for all types of cancer, including malignant gliomas, to study the potential enhancement of chemotherapy, radiotherapy, and surgery.

Appendix

Table A1. Top 10 Cancer Incidence and Mortality Among US Adults (per 100,000)

Incidence (per 100,000)		Mortality (per 100,000)	
Female Breast	124.8	Lung and Bronchus	40.6
Prostate	99.1	Female Breast	20.3
Lung and Bronchus	57.5	Prostate	18.9
Colon and Rectum	38.0	Colon and Rectum	14.0
Corpus and uterus, NOS	26.8	Pancreas	11.0
Melanomas of the Skin	22.1	Ovary	6.7
Urinary Bladder	19.5	Liver and Intrahepatic Bile Duct	6.6
Non-Hodgkin's Lymphoma	18.4	Leukemias	6.3
Kidney and Renal Pelvis	16.6	Non-Hodgkin's Lymphoma	5.5
Thyroid	14.5	Corpus and Uterus, NOS	4.8

Data source: (Centers for Disease Control and Prevention, 2018).

Table A2. 5-year Survival Rate (%) from Common Cancers among US Adults

Cancer Type (Males)	5-year Survival (%)	Cancer Type (Females)	5-year Survival (%)
Prostate	97.3 (97.2-97.4)	Thyroid	97.9 (97.8-98)
Testes	95.3 (95.1-95.5)	Melanomas of the Skin	92.3 (92.1-92.4)
Thyroid	93.3 (93.1-93.5)	Female Breast	88.6 (88.6-88.7)
Melanomas of the Skin	87 (86.8-87.1)	Hodgkin's Lymphoma	84.9 (84.5-85.3)
Hodgkin's Lymphoma	82.3 (81.9-82.7)	Corpus and Uterus, NOS	80.6 (80.5-80.8)
Urinary Bladder	76.1 (75.9-76.3)	Kidney and Renal Pelvis	72.1 (71.8-72.3)
Kidney and Renal Pelvis	70.7 (70.5-70.9)	Urinary Bladder	71.1 (70.8-71.4)
Non-Hodgkin's Lymphoma	66.2 (66-66.4)	Non-Hodgkin's Lymphoma	69.9 (69.7-70.1)
All Cancer Sites Combined	65.2 (65.2-65.3)	Cervix	67.6 (67.3-67.9)
Colon and Rectum	62.9 (62.8-63)	All Cancer Sites Combined	66 (66-66.1)
Larynx	59.7 (59.3-60.1)	Colon and Rectum	64 (63.8-64.1)
Oral Cavity and Pharynx	59.5 (59.3-59.7)	Oral Cavity and Pharynx	63.2 (62.9-63.6)
Leukemias	55.1 (54.8-55.3)	Larynx	56.6 (55.9-57.3)
Myeloma	45.5 (45.1-45.8)	Leukemias	54.2 (53.9-54.5)
Brain and Other Nervous System	31.4 (31.1-31.7)	Ovary	46.1 (45.9-46.4)
Stomach	26.8 (26.6-27.1)	Myeloma	45.1 (44.7-45.5)
Esophagus	17.9 (17.7-18.2)	Brain and Other Nervous System	34.3 (34-34.6)
Liver and Intrahepatic Bile Duct	16.6 (16.4-16.8)	Stomach	33 (32.7-33.4)
Lung and Bronchus	15.4 (15.3-15.5)	Lung and Bronchus	18.6 (18.2-18.9)
Pancreas	8.4 (8.2-8.5)	Liver and Intrahepatic Bile Duct	18.6 (18.1-19.1)
		Esophagus	18.6 (18.1-19.1)
		Pancreas	8.6 (8.4-8.7)

Data source: (Centers for Disease Control and Prevention, 2018).

Table A3. Incidence of Malnutrition in Various Cancer Types

Type of Cancer	Incidence of malnutrition (%)
Pancreatic carcinoma	83
Gastric carcinoma	83
Esophageal carcinoma	79
Carcinomas of the head and neck	72
Colorectal carcinoma	55-60
Pulmonary carcinoma	50-66
Prostate carcinoma	56
Mammary carcinoma	10-35

Data source: (Grober et al., 2016).

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