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REVIEW

Ketogenic Diets and their Therapeutic Potential on Breast Cancer: A Systemic Review

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Abstract: Breast cancer remains a major cause of morbidity and mortality in women, and there is still a lack of complementary approaches to significantly improve the efficacy of standard therapies. For many kinds of cancers, the usual standard care is the combination of surgery, radiation, and chemotherapy. However, this standard therapy is not effective alone. Therefore, new approaches that increase therapeutic effectiveness are urgently needed. The ketogenic diet is a novel therapeutic approach for certain types of cancers, as indicated by several preclinical and clinical evidences. The ketogenic diet, which consists of a high-fat, low-carbohydrate diet with adequate protein, appears to sensitize most cancers to standard therapy by utilizing the reprogrammed metabolism of cancer cells, making it a promising candidate for adjuvant cancer treatment. The majority of preclinical and clinical studies argue that the use of a ketogenic diet in combination with standard therapies is based on its potential to improve the antitumor effects of conventional chemotherapy, its overall good safety and tolerability, and quality of life improvement. According to new evidence, a ketogenic diet lowers the level of glucose and insulin in the blood, which are necessary for tumor growth. Thus, the ketogenic diet has emerged as a potential treatment option for a variety of cancers, including breast cancer. Besides, implementation of a Ketogenic diet in the clinic could improve progression-free and overall survival for patients with breast cancer. This review summarizes the composition and metabolism of ketogenic diets and their potential mechanisms in breast carcinogenesis in addition to their therapeutic potential on breast cancer.

Keywords: ketogenic diet, breast cancer, adjuvant breast cancer therapy

Background

Breast cancer is a malignant tumor that begins in the cells of the breast and spreads to other parts of the body.[1] It continues as a significant cause of morbidity and mortality in women. According to the American Cancer Society, the number of new cases and deaths from breast cancer in United States women in 2019 is estimated to be 268,600 and 41,760, respectively.[2] Indeed, 30% of all female cancers will be caused by breast cancer alone. Although the incidence of breast cancer in black women is lower than in white women, the death rate in black women is 41% higher than in white women, possibly due to diet and lifestyle.[3] Given the variability of lifestyle factors, epigenetic regulation, and genetic mutations, it is clear that a heterogeneous population is represented by individuals with breast cancer. Increased adiposity, estrogen or hormonal axis shift, and epigenetic signals significantly modulate the risk of breast cancer, all of which are in turn driven or substantially modified by dietary factors.[4] Currently most nutritional cancer work has concentrated on low-fat eating patterns or studying single anti-carcinogenic foods/nutrients, but the empirical or experimental evidence

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supporting these cancer management approaches is highly inconsistent. When carbohydrate and protein intake provide less than 20% of total energy expenditure (ie, a ketogenic diet (KD)), insulin levels and glucose availability are reduced, and hepatic ketone production is accelerated, resulting in a state of nutritional ketosis.[5]

In a cancer cell, the rate of glucose uptake dramatically increases, and lactate is produced, even in the presence of oxygen and fully functioning mitochondria. This process is known as the Warburg Effect.[6] Increased glycolysis and decreased tricarboxylic acid (TCA) cycle and oxidative phosphorylation (OXPHOS) activity are seen very early in tumorigenesis and form one of the hallmarks of cancer.[7] In line with the Warburg effect, it has been shown that breast cancer possesses high levels of glycolytic activity.[8]

Several studies have tested supplements and dietary elements as preventive agents for cancer. However, limited studies have concentrated on the use of diet as adjuvant therapy for cancer. The ketogenic diet is one of those adjuvant therapies. This diet includes high levels of fat, very low carbohydrates, and moderate levels of protein.[9] This composition shifts the body's metabolism toward the burning of fat rather than carbohydrates. Fatty acids are oxidized into ketone bodies (β-hydroxybutyrate (BHB), acetoacetate, and acetone) in the liver after ingestion of a ketogenic diet, which are then transported through the circulation to various tissues in the body where they are converted to acetyl-CoA. The net result of consuming KD is a modest reduction in blood glucose, high levels of ketone bodies, and greater glycemic control.[10]

Several studies have been conducted to assess the efficacy of KDs against various cancers. In animal models of malignant glioma,[11] breast cancer,[12] and colon cancer,[13] the diet reduced tumor size and improved survival. In clinical studies, tumor size reduction of advanced-stage malignant astrocytoma after KD was shown to be 21.8%. The combination of a KD with standard treatment resulted in improvement in female patients with glioblastoma multiforme.[14] In this review, the basics of KD, its proposed antitumor mechanisms in breast cancer, and currently available evidence from preclinical and clinical studies on efficacy are summarized.

Composition of Ketogenic Diets

The KD mainly consists of high-fats, moderate proteins, and very-low-carbohydrates. It can be divided into four main types namely, classical KD, medium-chain triglyceride diet, modified Atkins diet, and low glycemic index treatment.[15] Various dietetic approaches can produce a metabolic ketosis state such as classical KDs, fasting periods, or severe calorie restriction. Ketosis can be achieved through fasting-based interventions is known as fasting ketosis (FK).[16] The FK was used as an indicator of the effectiveness of weight loss.[17] Besides, ketosis also occurs in situations where total energy expenditure is equal to caloric intake; particularly in a diet that contains a high percentage of fat (> 60%) and/or low carbohydrates. This state of ketosis is known as nutritional ketosis (NK).[16]

NK has been studied as an epilepsy treatment because ketones are thought to provide energy to the brain, which decreases epileptic seizures. Furthermore, ketosis buildup capability resulting from a combination of NK and FK has been associated with effective weight loss and positive health outcomes.[18]

Recently, KDs have gained increased interest in the treatment of a variety of diseases, either as a stand-alone metabolic therapy or as part of a broader therapeutic approach. Chronic systemic diseases such as cancer, which have strong metabolic characteristics, are theoretically ideal targets for ketogenic metabolic therapies.[19]

Ketogenic Diet in the Treatment of Breast Cancer

Antitumor effects of the ketone bodies such as acetoacetate and BHB) have been observed in vitro in several breast cancer cell lines. However, it seems rather unlikely that the antitumor properties of KDs are solely attributable to the antiproliferative effects of ketone bodies and low blood glucose levels.[20,21]

The Current methods in vitro cancer cell culture commonly use high glucose, 25 mM (450 mg/dL), in the growth medium. While high glucose medium creates an optimal environment for cancer cell proliferation, these glucose levels may complicate the interpretation of drug efficacy studies.[22]

Preclinical Evidence

Numerous preclinical studies have shown that KDs have an anti-tumor effect, although, in certain cancer models, some studies have reported pro-tumor effects or serious side effects.[22,23] In most preclinical studies, KD slowed the growth of tumors, prolonged survival, delayed tumor initiation, and reversed cancer-induced cachexia process.[24,25]

Also, a study on various models of mouse cancer, including pancreatic, bladder, endometrial, and breast

cancer, as well as acute myeloid leukemia, showed that KD improves the effectiveness of targeted therapy, particularly inhibitors of PI3K, and overcomes drug resistance.[26] This suggests that KD could be part of a multimodal treatment regimen to improve the efficiency of classical cancer treatment.

Furthermore, studies on mice breast cancer models show that the concentrations of blood glucose and insulin in mice ingesting the KD were significantly lower. Strict insulin inhibition can lead to two main effects, both of which have the potential to induce the programmed death of cancer cells and reduce the proliferation of cancer cells. First, the decreased blood insulin levels at the cancer cell membrane result in less binding to the insulin receptor with resulting downstream inhibition of both the mammalian target of rapamycin (*mTOR*) signaling cascade,[25] and mitogen-activated protein kinase (MAPK) pathway.[27]

Therefore, reduced insulin concentration due to a ketogenic diet contributes to the potential to enhance programmed cell death by inhibiting the mTOR cascade and reducing proliferation via both pathways.[28] Second, hepatic ketogenesis due to insulin inhibition increases the blood levels of the BHB and acetoacetate ketone bodies, both of which have demonstrated histone deacetylase inhibitor effects at the cellular level which is known to be able to reduce the proliferation of cancer cells and improve the programmed death of cells.[29,30] Based on preclinical observation; in the breast cancer mouse model, a ketogenic diet inhibits the growth of primary breast tumors and lung metastases and prolongs the lifespans of a mouse. Further, when KD is combined with rapamycin, the KD can enhance the effects of rapamycin, to control cancer more effectively.[12,31] Based on the findings of these preclinical studies, KD exerts beneficial effects on breast cancer models. So that, many clinical studies are currently being performed on patients with breast cancer.

Clinical Evidence

For many kinds of cancers, the usual standard care is the combination of surgery, radiation, and chemotherapy.[32] However, there is no effective standard therapy available for highly aggressive cancer types with poor prognoses, such as triple-negative breast cancer.[33] Therefore, new approaches that increase therapeutic effectiveness are urgently needed. KD is a novel therapeutic approach for certain types of cancers, as indicated by preclinical evidence.[34]

A summary of clinical trial studies assessing a ketogenic diet as adjuvant therapy for breast cancer is shown in Table 1. KD led to a significant reduction in stage and tumor size compared to the control group. The tumor size in the KD group demonstrated a significant reduction compared to the baseline; a decrease in tumor size of 27 mm in the intervention group compared with 6 mm in the control group. Likewise, lymph node scores (N1, N2, N3) decreased in the KD group from baseline to the end of the study. This trend was not observed in the control group.[35]

In addition to its direct effects on tumor growth, KD has the potential to improve both patients' overall health status and their quality of life. A randomized controlled trial study on breast cancer patients reported that MCT-based KD caused a decrease in FBS (fasting blood sugar) as well as a rise in blood ketone levels in the intervention group. A positive effect on lipid profile as well as renal and liver markers was also observed. Moreover, it can be speculated that a KD with a high level of fat and a limited level of carbohydrates could affect the composition of the body. In this regard, it has been shown that a significant decreasing trend in body weight, BMI (body mass index), and body fat percentage in the intervention group, indicating a beneficial effect of MCT-based KD for breast cancer patients.[36]

According to the findings of randomized controlled trial studies on breast cancer, the level of adherence to the KD intervention indicates that a diet is a viable option for women with breast cancer who are taking chemotherapy.[35,36] However, some discomforts such as weakness, hunger, and lack of energy were observed in some patients along with the appropriate tolerability of the KD, which may be attributable to the following reasons. First, combining KD with chemotherapy can cause possible side effects, such as weakness and the likelihood of non-compliance. Second, it may be due to the oily diet, with a limited/eliminated level of foods containing carbohydrates such as fruits, milk, bread, rice, and sweets. Because of these, patients were not permitted to eat more than the prescribed diet and felt hunger particularly during the first two weeks of follow-up.[36] Nevertheless, several studies have reported good tolerability of KD in patients adhering to the diet and have concluded that the use of KD is feasible and safe in patients with breast cancer.[35]

A woman with triple-negative breast cancer who provided a combination of KD with metabolically supported

Table 1 The Clinical Trials Studies Assessing a Ketogenic Diet as Adjuvant Therapy for Breast Cancer

Design	Participants	Interventions	Follow-Up (Duration)	Outcomes	References
RCT	518 women patients with metastatic Her-2 negative breast cancer (n=259 on Ketogenic diet + irinotecan combined treatment and n= 259 on irinotecan monotherapy + normal diet as a control group)	Ketogenic-Diet	The follow up was before drug administration, during treatment, 4 weeks after treatment completion, and every 3 months (beginning 2 months after treatment completion)	In this trial, the ketogenic diet does not enhance the sensitivity of such patients to irinotecan therapy and does not affect target-lesion remission	Yan Wang et al., 2020[37]
Prospective cohort study	N= 63 (32 radiotherapy + KD and 31 on radiotherapy only as control groups)	Ketogenic-Diet	The median study duration (time from the start of radiotherapy until final measurement) was 35 days and 35 days in the SD group	In this clinical trial, a KD in a breast cancer population during radiotherapy improved body composition compared to control groups. and the KD intervention during radiotherapy was well accepted by the women who started it.	Rainer et al., 2020[38]
RCT	A total of 80 patients undergoing treatment with chemotherapy were randomly assigned to KD or control group for 12 weeks	Ketogenic diet	For 12 weeks.	KD in breast cancer patients has beneficial effects through decreasing TNF-α and insulin and increasing IL-10. And result in a better response through reductions in tumor size and downstaging in patients with locally advanced disease	Adeleh Khodabakhshi et al., 2020[35]

chemotherapy, hyperthermia, and hyperbaric oxygen demonstrated a complete clinical, radiological, and pathological response.[33]

Moreover, KD led to a significant reduction in stage and tumor size compared to the control group. The tumor size in the KD group demonstrated a significant reduction compared to the baseline; a decrease in tumor size of 27 mm in the intervention group compared with 6 mm in the control group. Likewise, lymph node scores (N1, N2, N3) decreased in the KD group from baseline to the end of the study. This trend was not observed in the control group.[35]

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Potential Mechanisms of the Ketogenic Diet in Inhibition of Breast Cancer

In the following sections, the potential mechanisms of KD action in breast carcinogenesis have been discussed.

Ketogenic Diet Targeting Glucose Metabolism of Breast Cancer Cells

Most solid cancers share metabolic characteristics such as increased glucose uptake and glycolysis dependence.[39] In breast cancer, aerobic fermentation (Warburg effect) is a common metabolic phenotype regardless of histopathological type, grade, or profile of gene expression.[40] In the Warburg effect, cancer cells mainly use glycolysis for energy production, coupled with lactate production,

paradoxically even if there is sufficient oxygen for respiration.[39] Consequently, The Warburg effect in cancer cells could be hypothesized to be at least partly targeted by creating chronic metabolic stress due to low glucose supply caused by dietary intervention with a KD and/or calories restriction.[41] The KD reduces activity in insulin-like growth factor-1 (IGF-1)/insulin–PI3K–Akt–mTOR signaling pathways which are strongly linked with the growth of breast cancer.[35,42] The insulin-activated enzyme PI3K frequently shows enhanced activity in various types of cancer, including breast cancer, due to PI3K gene mutations. Consequently, PI3K inhibitors are assumed to be potent anticancer drugs. However, the clinical trial has been revealed that targeted PI3K drugs often cause hyperglycemia leading to increased insulin levels and reactivation of the PI3K pathway, which eventually ends in treatment resistance.[43]

Recently, KD has been shown to improve the efficacy of anti-PI3K treatment and drug resistance by restricting the acute glucose-insulin feedback by PI3K inhibitors, thus blocking this loop.[24] Besides, in patients who strictly used KD, a reduction in lactic acid levels and transketolase-1 was reported.[44]

Ketogenic Diet Targeting Mitochondrial Metabolism of Breast Cancer Cells

Emerging evidence suggests that most cancers show deranged energy of metabolism. It is well documented that tumor cells, including breast cancer tissue, have abnormalities in the number, structure, and function of their mitochondria in most cancerous tissues, such aberrations would compromise the efficient production of energy.[45] Breast cancer cells also express abnormalities in mitochondrial-associated membranes in addition to abnormalities in mitochondrial membranes, which would further reduce energy production through OXPHOS. To maintain sufficient energy for breast cancer viability and growth, increased fermentation metabolism would be necessary to compensate for OXPHOS deficiency.[46,47] Substituting glucose by ketone bodies demands that the tumors have functional mitochondria to be able to use ketone bodies effectively for growth and survival.[42] The ketogenic diet is a non-pharmaceutical method of inducing the shift from glycolysis to mitochondrial respiration. Increased β-oxidation and mitochondrial biogenesis, increased antioxidant signaling via nuclear factor erythroid 2- related factor, and upregulation of manganese-dependent superoxide dismutase, catalase, and Mitochondrial uncoupling protein 2 are among the effects.[49,50]

Ketogenic Diet Targeting Reactive Oxygen Species (ROS) Production

Impaired OXPHOS leads to the accumulation of reactive oxygen species along with compensatory fermentation. ROS are carcinogenic and mutagenic and are largely responsible for tumor cell genomic instability and mutations. In other words, the mutations seen in tumor cells originate as a result of impaired energy metabolism.[51]

Oncogenes such as hypoxia-inducible factor 1-alpha (HIF-1α), myelocytomatosis (Myc), rat sarcoma, etc. facilitate the dependence of tumor cells on glucose and glutamine, while defects in the p53 and pRb tumor suppressor genes compromise the function of OXPHOS, thereby causing additional growth dependence on fermentation. These gene mutations are linked, through mitochondrial dysfunction, to breast cancer and other cancers.[52] The ketogenic diet may reduce both the induction and effectors of the Myc pathway, which is responsible for the transcription of lactate dehydrogenase A (LDH-A). The enzyme LDH-A is responsible for the conversion of pyruvate to lactate and forces a cell towards a Warburg-like Effect.[52,53]

Also, a clinical study reported that KD, hyperthermia, and hyperbaric oxygen therapy (HBOT) also targeted the defective energy metabolism of tumor cells. Hyperthermia contributes to a therapeutic effect by helping drug uptake, increasing the production of oxygen radicals, and inhibiting deoxyribonucleic acid (DNA) repair in cancer cells, leading to cancer cell death.[54] HBOT targets tumor hypoxia, which is related to tumor aggressiveness and resistance to chemotherapy and radiotherapy.[55] The dependence of tumor cells on glycolysis, a major contributor to the upregulation of antioxidant activity responsible for the increased resistance of the tumor to pro-oxidant chemotherapy and radiation therapy, is also exploited by both hyperthermia and HBOT. Consequently, hyperthermia and HBOT in the tumor cells will selectively increase oxidative stress. The metabolism of the major circulating ketone body, BHB, protects normal cells from this stress by reducing reactive oxygen species (ROS) production, while simultaneously elevating oxidative stress in tumor cells.[19] In general, the mechanisms of the ketogenic diet in cancer inhibition and the outcome of the patient are described in (Figure 1).

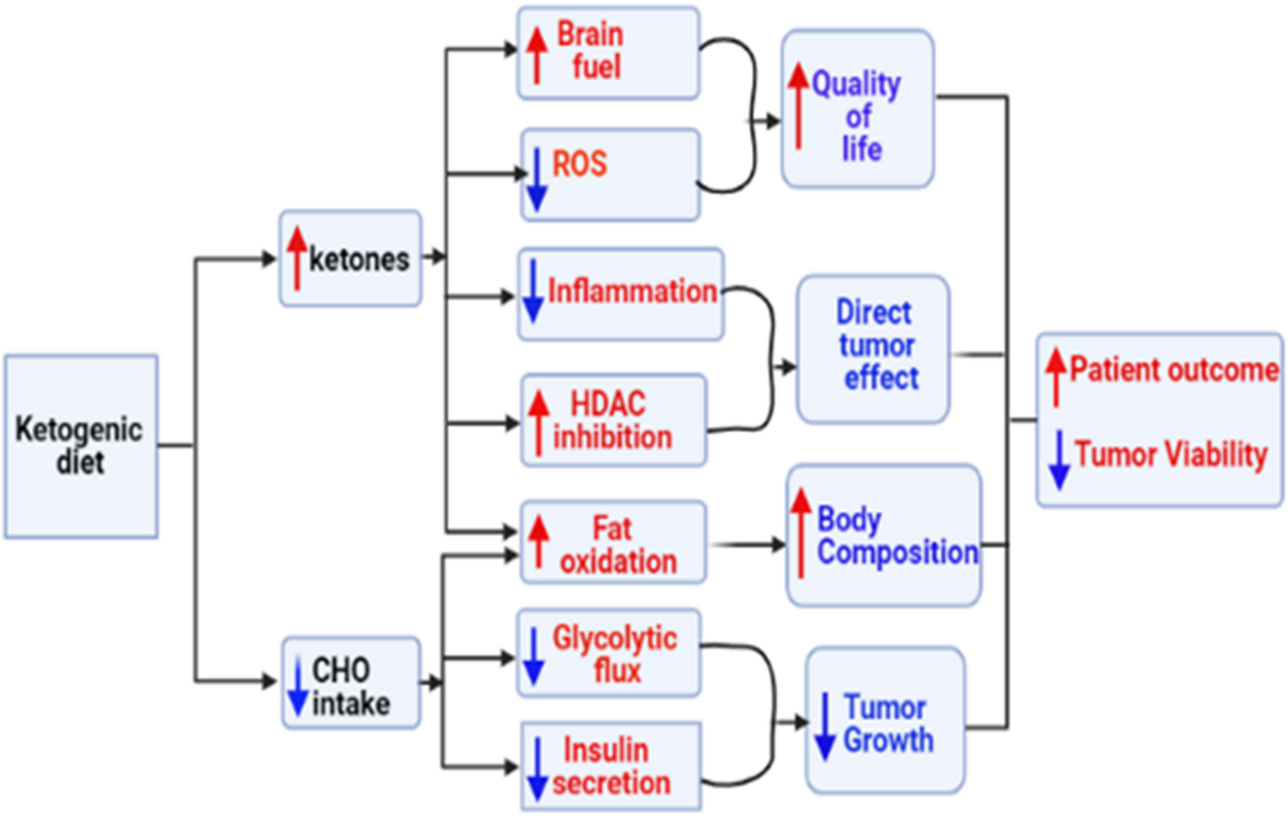

Figure 1 Pleiotropic mechanisms associated with the ketogenic diet and related tumor and patient outcomes.
Abbreviation: CHO, carbohydrate; HDAC, histone deacetylase; ROS, reactive oxygen specie.

Potential of the Ketogenic Diet as an Adjuvant Breast Cancer Therapy

As this review explains, KD appears to create an unfavorable metabolic environment for the proliferation of breast cancer cells and consequently, represents a promising adjuvant for a multifactorial therapeutic regime specific to patients. One clear benefit of the KD is its potential to increase the response to therapeutic drugs, which has been widely demonstrated in vitro and vivo.[22,26,48] Therefore, combining the KD with standard therapy or even novel treatment approaches to improve the therapeutic response in humans should be a research focus in this field.[56]

KD has been used in combination with low dose chemotherapy and other treatments to manage tumor growth in a woman with stage IV triple-negative breast cancer. The woman responded well and initially reported a complete therapeutic response to the combined treatment. Even though overall survival exceeded the median expected for her stage and grade, she ultimately succumbed to her cancer. A failure to proceed with the KMT protocol was deemed to be partially responsible for her tumor recurrence.[30] Besides, a case study of a woman with metastatic breast cancer (bone and lung metastases) revealed that one year of a ketogenic diet in combination with standard of care therapies resulted in complete remission, and no visible tumors were assessed via *fluorodeoxyglucose* -positron emission tomography.[57]

KD, initiated shortly after diagnosis and before surgery, may prove to be a non-toxic adjunct treatment capable of degrading the aggressive and invasive nature of cancer, thus increasing the efficiency of subsequent therapies.[58] The improvements in the selection, dosage, timing, and scheduling of drugs, diet, subsequent treatments, and procedures will provide benefits in survival and quality of life to patients with advanced metastatic breast cancer when used as a complementary or alternative therapeutic strategy alongside the standard of care.[52]

The press-pulse therapeutic strategy for cancer management is demonstrated with calorie-restricted ketogenic diets (KD-R) used in combination with drugs and procedures that create both chronic and intermittent acute stress on tumor cell energy metabolism while protecting and enhancing the energy

metabolism of normal cells. Eradication of breast tumor cells with minimal patient toxicity will be facilitated by optimization of the dosing, timing, and scheduling of KD used together with synergistic drugs and procedures. This therapeutic approach can serve as a framework for the design of clinical trials for the non-toxic management of most cancers, including breast cancer.[19] Given these lines of evidence indicating that nutritional ketosis is likely to have benefits for breast cancer patients, including direct effects on tumor pathways and viability, greater well-controlled interventions are required. However, the principles of a well-formulated ketogenic diet must be understood and implemented to ensure maximum safety and efficacy in terms of reducing tumor burden, managing comorbidities, and ensuring long-term quality of life.[57]

Conclusion and Future Perspectives

The use of KD as adjuvant therapy for breast cancer is supported in most preclinical and some clinical trials. Based on compelling evidence that ketogenic diets are associated with a wide range of health-promoting outcomes working through various mechanisms of action, a broader perspective has now emerged. The ketogenic diet causes less reliance on the glucose/insulin axis and significant changes in substrate use, such as increased fatty acid oxidation and decreased glucose flux, which could be a therapeutic mechanism for the treatment of breast cancer.

Ketogenic diets also restore the hormonal and inflammatory environment of the host, which is thought to suppress tumor growth. The activation of growth factors and oncogenic pathways involving PI3K/Akt and mTOR should be reduced as insulin concentration and signaling are reduced. The ketogenic diet encourages an anti-inflammatory phenotype, which may result in less invasiveness and longer progression-free survival. Generally, patients with breast cancer can benefit from a ketogenic diet because it improves biochemical parameters and body composition.

To better understand the mechanisms behind KD therapy and its use in breast cancer management, more molecular and well-designed randomized controlled trials are needed. Also, Large-scale clinical trials focusing on the implementation of a well-formulated ketogenic diet for various types of breast cancer will be conducted. Furthermore, additional clinical trials are needed to elucidate whether calorie restriction or the combination with other therapeutic modalities like radiotherapy or anti-angiogenic treatments, can improve the efficacy of the ketogenic diet.

Abbreviation

BMI, Body mass index; CHO, Carbohydrate; FBS, Fasting Blood sugar; FK, Fasting Ketosis; HBOT, Hyperbaric oxygen therapy; HDAC, Histone Deacetylase; HIF-1α, Hypoxia-inducible factor 1-alpha; IGF-1, Insulin-like growth factor-1; KD, Ketogenic diet; KD-R, Calorie Restricted Ketogenic Diets; KMT, Ketogenic metabolic therapy; MCT, Medium-Chain Triglyceride; NK, Nutritional Ketosis; OXPHOS, Oxidative Phosphorylation; PI3K, Phosphatidylinositol-3 Kinase; Ras, Rat sarcoma; ROS, Reactive Oxygen Species; TCA, Tricarboxylic Acid.

Data Sharing Statement

Supporting data is available from the corresponding author on reasonable request.

Ethics Approval

Ethical approval is not applicable since the publication is based on the data that was previously published articles and not on its investigations.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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