

Ketogenic Diet in Cancer Prevention/Therapy

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The ketogenic diet (KD) has recently emerged as a metabolic therapy in cancer treatment, targeting cancer cell metabolism rather than a conventional dietary approach. The ketogenic diet (KD), a high-fat and very-low-carbohydrate with adequate amounts of protein, has shown antitumor effects by reducing energy supplies to cells. This low energy supply inhibits tumor growth, explaining the ketogenic diet's therapeutic mechanisms in cancer treatment.

alternative cancer therapies

anticancer diet

targeting cancer metabolism

calories restriction

1. Introduction

Cancer, “the sickness of the century”, is one of this era's leading causes of mortality worldwide, which is becoming more threatening day by day due to the increasing number of cancer cases and the ability of this disease to resist the existent therapeutic and pharmacological approaches. In the year 2020 and in the United States alone, 1,806,590 new cancer cases were discovered according to the American Cancer Society, with 606,520 cancer deaths ^[1]. With approximately 89,500 new cancer cases per year and 9270 deaths in adolescents and young adults ^[2]. The conventional interventions such as surgery, chemotherapy, hormonal therapy, radiation therapy, monoclonal antibodies, and tyrosine kinase inhibitors were able to eliminate some types of cancers, induce cancer regression and inhibit the growth of some others ^[3]. Nevertheless, each one of these interventions has its own limitations that can be an obstacle to both healthcare providers and patients to reach the desirable objectives; for example, the advanced stage of cancer and metastasis level renders the surgical procedure unreasonable and not effective. In addition, both chemotherapy and radiation therapy have cancer induction effects that may lead to secondary tumors and various toxicity issues inducing normal-tissue complications; these factors and others put pressure on the medical body to find new, safe, and cost-effective cancer therapy agents ^[3].

The metabolic differences between normal cells and cancerous cells is not a new subject, especially after the discovery of the Warburg effect by Otto Warburg in 1920s ^{[4][5][6]}, and the formulation of his hypothesis in 1956. Based on his hypothesis, cancer cells have irreversible damage in cell respiration and dysfunction in the mitochondria, making them dependent on fermentation to obtain ATP ^{[7][8][9][10]}. Further studies suggested that this process is more important for the production of substantial building blocks for cancer, which means it is associated with cell proliferation and cancer growth ^{[11][12]}.

Consequently, in the last few years, there has been a strong direction by researchers to find or develop a diet-based strategy as a new complementary therapy that affects cancer cells' metabolic pathways. Intermittent fasting,

prolonged fasting, ketogenic diet (KD), fasting-mimicking diet and alternative caloric restrictions are dietary approaches that are being studied with many clinical and animal trials available to prove their efficacy and ability to, at least, be used as prophylactic or adjuvant strategies in cancer treatment [\[13\]](#)[\[14\]](#)[\[15\]](#)[\[16\]](#)[\[17\]](#)[\[18\]](#)[\[19\]](#).

A ketogenic diet (KD) causes a metabolic shift from glycolysis into mitochondrial metabolism, the differential stress resistance phenomenon with high tumor control ability and lower normal-tissue complications [\[17\]](#), which makes the ketogenic diet an interesting dietary approach for cancer patients under supervision and follow up of a healthcare provider. The ketogenic diet content is distinguished by high fat, moderate to low protein and very low carbohydrate intake. The macronutrient distribution of KD is about 90% fat, 2% carbohydrate, and 8% protein. This is achieved by following the standard fat to carbohydrate and protein ratio of 4:1 and 3:1, respectively [\[20\]](#). Another recent study has suggested that the clinical use of KD is composed of at least 80% fat with a KD ratio of 2:1 to 3:1 [\[21\]](#). The low intake of glucose accompanied by high fat and adequate protein content causes a reduction in IGF1 and an increase in ketosis or ketone body production in human clinical studies [\[18\]](#). Moreover, multiple studies have also supported that carbohydrate restriction has a protective effect against cancer in animal models [\[22\]](#)[\[23\]](#)[\[24\]](#)[\[25\]](#). The use of a ketogenic diet was reported to show improvement in a patient condition in one of two girls with advanced astrocytoma, and this observation may be explained on the basis that brain tumors are incapable of using ketones as an energy source in comparison with healthy brain tissue [\[26\]](#). However, results from other clinical studies indicated that sufficient therapeutic activity was not achieved when a ketogenic diet was used as the only treatment in patients with cancer. These results suggest that to achieve the potential benefits of such diets, they should be used in combination with other treatment strategies, including chemotherapy, radiotherapy, antiangiogenic treatments, PI3K inhibitors, and fasting-mimicking diet [\[22\]](#)[\[27\]](#).

2. Cancer Metabolism and Warburg Effect

Cancer metabolism refers to the alterations in cellular metabolism pathways that are evident in cancer cell in comparison with most normal tissue cells and is one of the fundamental hallmarks of cancer [\[28\]](#).

This characteristic and profound metabolic alteration is mainly driven by oncogenic signaling pathways and also by amplified or alternatively spliced metabolic enzymes, which allows cancer cell accommodation to metabolic demands needed to sustain cell growth, proliferation, and survival in an environment with fluctuating nutrient levels. Nevertheless, this alteration makes cancer cells dependent on a constant supply of nutrients and energy in addition to the studied deregulated glucose metabolism, which leads to the production of more amino acids and fatty acids, thus increasing fuel tumor cell growth [\[29\]](#)[\[30\]](#).

A common characteristic of cancer cells is increased glucose uptake in order to support the production of intermediates needed for the synthesis of lipids, proteins, and nucleic acids. In addition, cancer cells via increased glutamine uptake and glutaminolysis are able to maintain a continuous supply of intermediates in the tricarboxylic acid (TCA) cycle that are diverted into biosynthetic reactions [\[31\]](#). This increased biosynthetic activity also requires an accompanying increased production of NADPH, which serves as a reducing agent for anabolic reactions and to maintain cellular redox balance [\[32\]](#). Furthermore, the epigenetic modifications that occur during the process of

cellular transformation and cancer progression are derived from metabolites such as acetyl-CoA for acetylation, NAD for deacetylation, SAM for methylation, α -ketoglutarate for demethylation, and UDP-GlcNAc for glycosylation [33]. Moreover, recent advances in the carcinogenesis process have revealed that cancer is a complex disease and that simple investigation of genetic mutations of cancerous cell is not adequate to understand it, and that cancer cells are present in a complex tumor tissue, communicate with the surrounding microenvironment, and develop traits that promote their growth, survival, and metastasis [34].

3. Ketogenic Diet as Cancer Therapy: Mechanisms of Action

The ketogenic diet (KD) is defined as a high-fat, low-protein, and low-carbohydrate diet and has been used in the treatment of several diseases. Moreover, KD can be considered inexpensive, safer, and easier to be carried out when compared to traditional anticancer therapy. Currently, the ketogenic diet (KD) offers an encouraging chance to be used either as a therapeutic diet or as an adjuvant cancer therapy in animal models and humans. The following section will discuss dietary adjustments (i.e., ketogenic diet) which is expected to enhance chemotherapy effects on tumor cells, protect healthy cells, lower inflammation, and regulate gene expressions of different proteins and factors including (matrix metalloproteinases (MMPs), histone deacetylases (HDACs), AMP-activated protein kinase (AMPK), pyruvate kinase (PK), and P53 [20][21][35][36].

4. Ketogenic Diet as a Prevention of Cancer

Cancer cells undergo various metabolic modifications to satisfy their need for energy, glucose, protein, and signaling to proliferate. Otto Warburg described that cancer cells require more glucose than normal cells to generate ATP [37]. Cancer activates several pathways to survive. Moreover, carcinogenesis is mediated by different agents including the high level of blood glucose, insulin, inflammatory, and pro-inflammatory factors [38][39].

Multiple lines of research suggest the use of ketogenic diets (KD) or, more broadly, high fat, low carbohydrate, and sufficient protein diets as cancer treatment or prevention methods, either alone or in combination with medicines [38][40]. Several studies have looked into the connection between diet and reducing the risk of chronic diseases, such as cancer and age-related diseases, as well as extending the lifespan [41]. Dietary changes target multiple pathways, including the insulin pathway, PI3K, AKT, mTOR, ketone bodies, adiponectin and leptin protein distribution, and IGF-1 [37][39][42][43][44]. Preclinical and clinical studies have demonstrated the anti-aging and anticancer effects of KD [45][46][47][48][49]. Physical exercise, in addition to diet management, has been shown to reduce cancer risk in most cancer types.

PI3K/Akt dysregulation is directly associated with neoplastic development, as well as increased resistance to cancer therapy, although PI3k promoted the downstream of both insulin receptor and IGF-1R [50]. The mechanistic (or mammalian) target of rapamycin (mTOR) is a serine-threonine protein kinase; mTOR signaling is regulated under a wide range of factors and circumstances [50]. It is stimulated by growth factors, mitogens, PI3K, activated AMP kinase, and hormones, including insulin [50]. Under low nutritional conditions, AMP-activated protein kinase

(AMPK), phosphatidylinositol 3-kinase (PI3K), and mTOR are all acutely affected [41]. KD stimulates the AMPK signaling pathway, the tumor suppressor activity, which leads to mTOR signaling inhibition [41][50].

One of the main concerns regarding a high-fat diet is the potential to induce inflammation due to the high amount of fats, especially saturated fats [43]. While various fat types can lead to pro- or anti-inflammatory responses, saturated fat mimics the actions of lipopolysaccharide (LPS), which causes inflammation when it binds with its receptor on the surface of macrophages/monocytes and other innate immune cells [43][51]. In contrast, polyunsaturated fats such as the omega-3 fatty acids, EPA and DHA, have been found to have anti-inflammatory properties [43][52]. Chronic inflammation is described as an increase in the release of inflammatory cytokines into the local and systemic circulation. Recently, inflammation has been considered a characteristic of cancer [53][54]. In many tissues and tumor types, a low carbohydrate, high-fat diet (with a concentration on unsaturated fats) reduces the amount of tumor-infiltrating macrophages, the levels of circulating and tissue cytokines, the NF- κ B signaling, and COX-2 expression [41]. Thus, the high anti-inflammatory activity of KD implemented a cancer prevention effect [41].

The metabolic outcome from consuming a ketogenic diet is the formation of ketone bodies, including hydroxybutyrate (β -HB), acetoacetate, and acetone [43][55]. A high concentration of β -hydroxybutyrate triggers an uncoupling protein-2 (UCP-2) in mitochondria [39], which protects cells from oxidative stress. On the other hand, its absence may cause an abundance of reactive oxygen species, the release of pro-inflammatory cytokines, and persistent activation of nuclear factor kappaB (NF- κ B) [39][55]. Thus, ketone bodies play a critical role in decreasing oxidative stress and extending the patient life cycle [43][55].

Adiponectin, leptin are peptide hormones produced from visceral white adipose tissue. Adiponectin has a negative correlation with leptin and other adipokines. Lower levels of adiponectin have been linked to type 2 diabetes, insulin resistance, metabolic syndrome, hypertension, cardiovascular diseases, and cancer. Several studies have demonstrated the protective role of the keto diet in decreasing the risk of cancer, reducing oncogenesis hormones, and extending the lifespan. Additionally, increased adiponectin, which activates several pathways such as AMPK, MAPK, and PI3K/Akt also reduces pro-inflammatory cytokine expression [41][56].

Finally, a direct connection was established between a high-calorie diet and the risk of cancer, as well as a way to proceed for cancer prevention by lifestyle modification such as physical activity and exercise, and healthy diets rich in fruit, vegetables, and whole grains, and low in red meat and saturated fats [55]. KD may not prevent the occurrence of a tumor, but it delays tumorigenesis and improves the survival rate [40][43]. Moreover, KD shows a synergistic effect on cancer treatment when combined with chemotherapy or other cancer therapies [40][50].

5. Ketogenic Diet as an Epigenetic Modifier in Cancer

Epigenetic modifications represent an essential step of gene transcription regulation. It has been observed that DNA methylation, miRNAs, and histone modifications occurred during the early stages of cancer progression and metastasis [57][58]. Recent studies have suggested that ketone bodies can organize cellular functions through innovative epigenetic modulation; β -hydroxybutyrylation, which integrates the DNA methylation; and histone

covalent post-translational modifications (PTMs) [59][60]. Interestingly, using a ketogenic diet enhanced adenosine production, which resulted in the blocking of DNA methylation [61][62]. Moreover, ketone bodies (β -hydroxybutyrate and acetoacetate) have an impact on epigenetic factors. They restrain the histone deacetylase 1 (HDAC1) activity, and promote PTMs of proteins by butyrylation, affecting DNA methylation and acetylating histone and non-histone proteins [57][62][63][64][65].

MicroRNAs (miRNAs) are endogenous small non-coding RNA sequences approximately 22 nucleotides in length [66][67][68] that regulate gene expression by binding with the target mRNA to regulate protein synthesis or degradation of the mRNA [69][70][71][72]. MicroRNA plays a part in a wide array of biological activities that involves cell differentiation, proliferation, death, metabolism, and balance of energy [66][73][74]. Various types of miRNAs have been linked to chronic disorders such as obesity, diabetes, and cancer [66][72][73][74], suggesting that they may operate as oncogenes or tumor suppressor genes [75]. MicroRNAs have been linked to cancer at all phases, including initiation, progression, apoptosis, angiogenesis, proliferation, and differentiation [67][71][76][77].

The miR-21 gene can be detected in the blood, bone marrow, liver, lung, kidney, gut, colon, and thyroid [78]. Many biological processes, including inflammation, fibrosis, and cancer, are controlled by miR-21 [79]. MicroRNA-21 (miR-21) is an oncogenic miRNA that is typically elevated in hepatocellular carcinoma (HCC) [80][81][82][83]. It promotes the release of inflammatory substances such as interleukin 6 (IL-6) [84], signal transducer, and activator of transcription 3 (STAT3)-dependent mechanism [85]. It also modulates growth factor (TGF-) via the SMADs signaling cascade [86]. Furthermore, MiR-21 contributes to cancer progression by targeting tumor suppressor mRNAs such as tropomyosin 1 [87], programmed cell death 4 (PDCD4) [88], phosphatase, and tensin homolog (PTEN) [89].

MiR-21 levels are also higher in the serum and plasma of multiple myeloma (MM) patients, considered to be used as a biomarker for the MM [90][91][92][93]. MiR-21 controls the expression of genes involved in MM proliferation, the G1/S transition, and invasion [94][95]. The KD significantly alters the expression of several microRNAs on tumor tissue from animals fed the KD versus those fed a standard rodent diet [69][96].

In breast cancer patients, the expression of various miRNAs discriminated tumors from normal tissue. MiR-10b, miR-125b, let-7, and miR-145 were significantly downregulated in malignant tissue, but miR-21 and miR-155 were overexpressed [67][97]. Another study found that overexpression of miR-335, miR-126, and miR-206 reduced metastasis from the breast to the lung or bone in mice [98][99]. INF- promotes the proliferation and spread of breast cancer cells through promoting the production of miRNA-23b and miRNA-27b, which is widely recognized as a hallmark of cancer [100]. According to many studies, the keto diet appears to have anti-inflammatory characteristics by contributing to the reduction of -TNF- expression through PPAR activation [100][101].

MiRNA changed several tumor-suppressive and oncogenic pathways connected to colorectal cancer (CRC), including Let-7, MiR-21, and MiR-145 [68]. In colorectal cancer cells, Let-7 miRNA operates as a tumor suppressor miRNA, influencing the expression of the Ras and c-myc genes, which are both critical in colon cancer development and progression [102][103][104]. In addition, the Let-7 miRNA regulates p53 [105][106][107]. Oncogenic miRNAs, such as MiR-21, are overexpressed in colon tumor tissues. MiR-21 is designed to restrict the expression

of the phosphatase and tensin homolog (PTEN) gene; however, a later study has revealed that it also suppresses other tumor suppressors such as programmed cell death 1 [71][108][109][110]. The role of miR-145 in colorectal cancer appears to be debatable. While it was previously thought to be a tumor suppressor miRNA in colorectal cancer due to its ability to target both the insulin receptor substrate-1 and the insulin-like growth factor receptor 1 (IGF-1), more recent studies have shown that upregulation of miR-145 can improve the ability of colorectal cancer cells to migrate and invade [71][111][112]. Environmental and lifestyle factors are prevalent causes of colorectal cancer [71]. One such element was that diets have been demonstrated to alter miRNA expression in patients with colorectal cancer [71].

MiRNAs have been demonstrated to affect many elements of the development of cancer and metastasis which can be used as biomarkers and therapeutic targets. Diverse dietary products, including nutrients (vitamins, minerals, fatty acids, etc.) and bioactive foods (curcumin, resveratrol, catechins, etc.), protect against cancer through modulating the expression of miRNA [67][71][92]. KD was also applied in animal and human models as an adjuvant cancer treatment. The impact of KD on reducing the development of the tumor and improving survival of malignant glioma models in animals has been demonstrated in preclinical trials by the modulation of miRs; this is also the case for prostate cancer, colon cancer, and gastrointestinal carcinoma [24][113][69][96][114]. KD increases the expression of several miRNAs, many of which have been shown to have tumor suppressor properties in glioma [72][115]. More in-depth mechanistic investigations are needed to determine the potential function of miRNA and the keto diet in the development of cancer.

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