

Ketogenic Diet and Cancer

Ketojenik Diyet ve Kanser

Duygu Doğan¹, Emine Okumuş², İsmet Meydan¹

¹ Van Yuzuncu Yil University, Health Services Vocational School, Van, Türkiye

² Van Yuzuncu Yil University, Faculty of Engineering, Department of Food Engineering, Van, Türkiye

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ABSTRACT

The ketogenic diet is a diet implemented with high fat consumption and adequate protein by reducing glucose and increasing ketone bodies. Ketogenic diet: it is recommended as an effective intervention on diseases such as diabetes, obesity, cardiovascular diseases and cancer. The ketogenic diet is a diet with high fat and low protein by reducing glucose and increasing ketone bodies. Ketogenic diet: it is recommended as an effective intervention on diseases such as diabetes, obesity, cardiovascular diseases and cancer. In experimental models and clinical studies, the ketogenic diet has an antitumor effect by reducing energy sources to cells and preventing tumor growth. Cancer cells use the Warburg effect on ketogenic diet metabolism. Aerobically dominant glucose utilization may be a possible pathway to be targeted during cancer therapy. Research emphasizes that the integration of the ketogenic diet with the traditional treatment protocol will show positive results on the antitumor effect of chemotherapy. This review provides evidence for understanding the mechanism of action of the ketogenic diet on cancer treatment and its therapeutic use

Keywords: Cancer, Ketogenic diet, Antitumor, Warburg effect.

ÖZET

Ketojenik diyet, glikozu azaltıp keton cisimlerini arttırarak yüksek yağ kullanımı ve yeterli miktarda protein ile uygulanan bir diyettir. Ketojenik diyet; diyabet, obezite, kardiyovasküler rahatsızlıklar ve kanser gibi hastalıklar üzerinde etkili bir müdahale olarak önerilmektedir. Deneysel modellerde ve klinik çalışmalarda ketojenik diyet, hücrelere giden enerji kaynaklarını azaltıp tümör büyümesini engelleyerek, antitümör etki göstermektedir. Kanser hücreleri ketojenik diyet metabolizması üzerinde Warburg etkisini kullanmaktadır. Aerobik olarak baskın glikoz kullanımı, kanser tedavisi sırasında hedef alınması gereken muhtemel bir yol olabilir. Araştırmalar ketojenik diyetin, uygulanan geleneksel tedavi protokolü ile bütünleşmesinin kemoterapinin antitümör etkisi üzerinde olumlu sonuçlar göstereceğini vurgulamaktadır. Bu derleme, ketojenik diyetin kanser tedavisi üzerindeki etki mekanizmasını anlamak ve terapötik olarak kullanımına ilişkin kanıtlar sunmaktadır.

Anahtar kelimeler: Kanser, Ketojenik diyet, Antitümör, Warburg etkisi.

* Corresponding author: Emine Okumuş. E-mail: emineokumus@yyu.edu.tr

ORCIDS: Duygu Doğan: 0000-0001-8338-9063, Emine Okumuş: 0000-0001-5266-8633, İsmet Meydan: 0000-0001-5640-6665

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INTRODUCTION

Ketogenic diet; it is a diet approach based on minimal carbohydrate intake and excessive fat intake, which causes weight loss, provides mental relaxation and increases energy levels (O'Neill and Raggi, 2020). In this diet, which increases fat and protein intake and reduces carbohydrate consumption, fat is used as the body's primary fuel source, which activates the metabolic process called ketosis (Masood et al., 2023). In this way, the body can keep enough calories for daily activity. The main purpose of this diet is to reduce the fat rate in the body and improve the metabolic health of the body in a positive way (Ding et al., 2019; O'Neill and Raggi, 2020). In recent studies on ketogenic diet; it has been stated that it has benefits on many diseases such as reversing the symptoms of metabolic syndrome, improving the epigenetic profile, changing the microbiome, reducing or eliminating the insulin requirements of type II diabetic patients, increasing brain function and reducing the risk of cancer (Dowis and Banga, 2021). The ketogenic diet has recently been proposed as an adjuvant therapy in cancer treatment (Klement, 2019). The effect of the ketogenic diet as an adjuvant for cancer is based on the mechanism of the Warburg effect (Weber et al., 2018). The Warburg effect is based on the process of cancer cells providing ATP, which is used as an energy source, through glycolysis, unlike oxidative phosphorylation. In this way, the ability of some cancer cells to metabolize ketone bodies is lost. Ketosis occurs when cells are unable to obtain energy through glycolysis. This causes a decrease in insulin and similar growth factors, which are among the factors that cause the increase of cancer cells (Yang et al., 2021). Recent studies have shown that the ketogenic diet has a curative effect on tumor control in glioma, pancreatic cancer, lung cancer, breast cancer and prostate cancer (Zhao et al., 2022). It has also been stated that it is not only effective on tumor growth, but also plays a role in making other cells less affected by radiotherapy and chemotherapy treatments (Klement, 2019). It can be predicted that this diet, which has proven beneficial effects, will provide improvements both in supporting cancer treatment and in improving the quality of life of cancer patients. This study conducted a systematic review to better understand the ketogenic diet and provide more information about its effectiveness as an adjuvant treatment for cancer.

Physiology of the ketogenic diet

The principle of the ketogenic diet consists of reducing carbohydrate consumption by keeping fat and protein intake higher. With this diet, carbohydrate intake decreases to less than 50 g per day (Shilpa and Mohan, 2018). In carbohydrate deprivation, insulin secretion decreases and glycogen stores in the body are depleted.

The body activates the metabolic process of gluconeogenesis and ketogenesis to provide a different energy source (Masood et al., 2023). Gluconeogenesis can be sustained for three days in the presence of a ketogenic diet, but when glucose production decreases, endogenous breakdown of glucose cannot provide sufficient energy. To meet the metabolic requirements of the body and brain, the process of ketogenesis begins to obtain an alternative energy source in the form of ketone bodies. In this case, ketone bodies are used as the primary energy source (Batch et al., 2020; Hernandez, 2021). Ketone bodies are produced in the liver as acetoacetate and β -hydroxybutyrate. These primary ketone bodies accumulate in the body and are used as an energy source in the presence of a ketogenic diet. Since ketone bodies are formed as a result of the breakdown of fats, ketosis is one of the safest parameters of fat loss (Shilpa and Mohan, 2018; Masood et al., 2023). Ketone bodies synthesized in the body can be used as an energy source by the heart, muscle tissue and kidneys, and can also provide alternative energy to the brain by passing the blood-brain barrier (Dhillon and Gupta, 2023).

Effect of ketogenic diet on cancer

Cancer is one of the most important challenges people face. Cancer occurs as a result of mutations in many genes that regulate cell growth and proliferation (Golemis et al., 2018). These mutations may be due to many reasons such as DNA replication defects, errors in DNA repair mechanisms, exposure to mutagens, and increase in reactive oxygen species (Dowis and Banga, 2021). Preventive mechanisms for cancer will aim to eliminate these causes or reduce cellular errors. Another underlying cause of deaths caused by cancer is obesity and overweight (Dowis and Banga, 2021). The role of obesity in cancer is the increase in fat cells in the body. In this way, insulin and insulin growth factor 1 (IGF1) hormones increase. These hormones activate signaling pathways that aim for greater cell survival and regulate transcription factors that have an important role in cell proliferation, as shown in Fig.1 (Font-Burgada et al., 2016). These two hormones increase the glucose level in the cells and provide the energy molecules required for cell growth. While insulin supports glucose uptake into cells, it also inhibits liver ketone production. Research conducted have shown that the increase in serum insulin level supports the growth of cancer cells (Gunter et al., 2015; Bolla et al., 2019; Dowis and Banga, 2021). It is inevitable that the diet can have a great impact on eliminating the risk of cancer, especially considering that it reduces body weight, reduces insulin levels and targets the metabolic weaknesses of cancer cells (Dąbek et al., 2020). While reducing the use of glucose through diet starves the cancer cell, ketone bodies become available for the energy needs of normal cells.

Another effect is that it reduces insulin and insulin-like growth factors that help cancer proliferate (Dąbek et al., 2020; Dowis and Banga., 2021). Ketogenic diet; it has shown its therapeutic effect on neuroblastoma, acute myeloid leukemia and glioblastoma tumors thanks to its ability to reduce GPR109A (nicotinic acid G-protein coupled

receptor) expression, activate mTORC1 (Mammalian Target of Rapamycin Complex 1) and reduce glucose uptake in the tumor (Tobias et al., 2015).

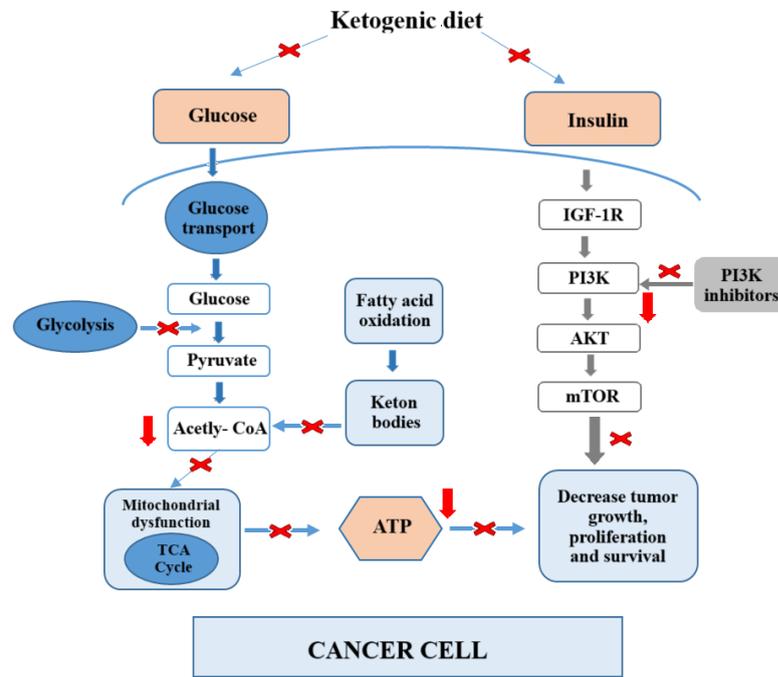


Figure 1. Effect of ketogenic diet on cancer cells. IGF-1R: Insulin growth factor; AKT: Protein kinase B; ATP: adenosine triphosphate; CoA: coenzyme A; IGF: insulin growth factor: mTOR: mammalian target of rapamycin; PI3K: phosphatidylinositol-3-kinase; TCA: tricarboxylic acid (Sims et al., 2023).

Ketogenic diet and the Warburg effect

Cancer cells can be identified by metabolic changes that result in excessive glucose intake. This change is explained by the Warburg effect, which is defined as an increase in aerobic glycolysis for ATP production (Klement, 2019; Tan et al., 2020). Additionally, in the absence of oxygen, oxidation plays a serious role in the ATP production of cancer cells, thanks to the production of lactate from the fermentation of glucose. Apart from this, cancer cells cause excessive ROS production as a result of the electron transport system not working. Glucose, the main component of the tumor, is required for

both cell survival and proliferation. Therefore, the ketogenic diet becomes a therapeutic approach by reducing the glucose level of cells and increasing the level of unused ketone bodies, which are the substrate for ATP production by cancer cells (Talib et al., 2021). While the ketogenic diet starves tumor cells, normal cells are subjected to prolonged glucose restriction, resulting in fatty acid oxidation, which plays an important role in ketone bodies synthesis. It is subsequently converted to Acetyl-CoA and enters the TCA cycle to produce ATP. In this way, ketone bodies support normal cells to stay healthy, as shown in Fig. 2 (Wallis, 2018; Tran et al., 2020; Talib et al., 2021).

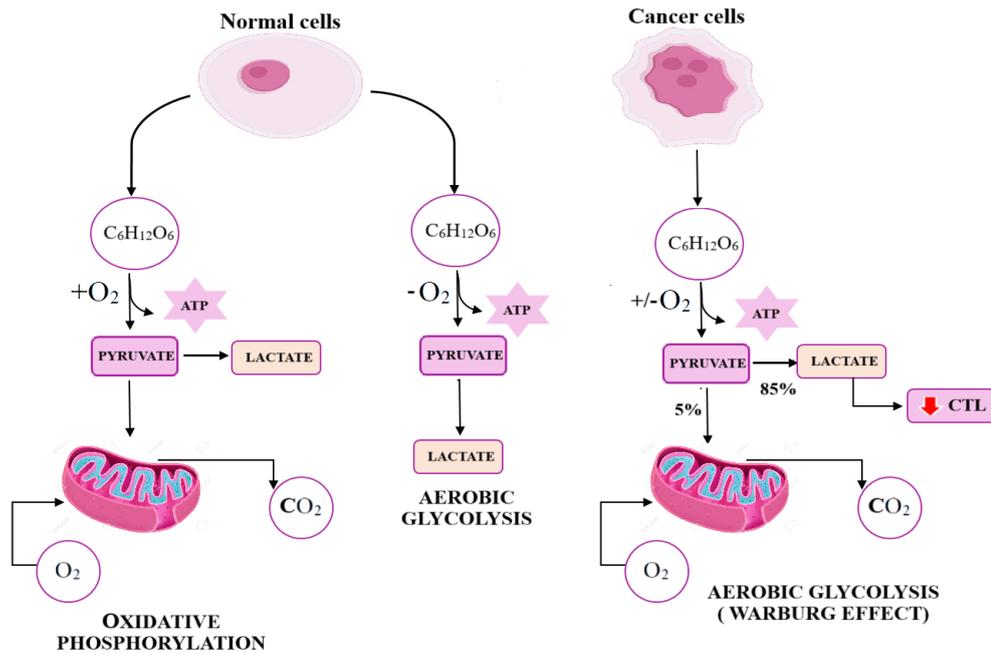


Figure 2. Warburg effect in cancer cells (Toadere et al., 2024). CTL: Cytotoxic T lymphocytes.

Preclinical and clinical studies

Poff et al, investigated the effect of a ketogenic diet in mice with systemic metastatic cancer. As a result of the study, it was determined that the ketogenic diet alone significantly reduced blood glucose, slowed tumor growth and increased the average survival time in cancerous mice by 56.7% (Poff et al., 2013). In another study, the effects of ketone bodies on pancreatic cancer were examined, and it was stated that glycolytic flux in tumor cells decreased after treatment with ketone bodies. It has been stated that ketone bodies induce apoptosis and reduce glutamine uptake, ATP content and survival in multiple pancreatic cancer cells. Ketone bodies have been found to significantly reduce cachexia in cell line models (Shukla et al., 2014). Gluschnaider et al studied mammary tumor interaction on transgenic mice. It has been stated that the ketogenic diet applied reduces tumor progression by suppressing tumor formation. This may suppress the esterification of free long-chain fatty acids into lipids due to the limiting effect of insulin and glycerol-3-phosphate, thus showing its natural tumor suppressor effect (Gluschnaider et al., 2014). The ketogenic diet has been evaluated as a new treatment in the mouse model of peritoneal dissemination of BALB/c mice. To achieve experimental peritoneal dissemination, the mouse colon adenocarcinoma cell line colon 26 was inoculated. After tumor inoculation, mice were fed a ketogenic diet, and the study showed increased survival and improved health status. It is thought that the ketogenic diet may be a preventive treatment for peritoneal spread (Kasumi and Sato, 2019). 29 patients with breast cancer who followed a ketogenic diet were compared with 30 patients who consumed their standard diet before, in the middle, and at the end of radiotherapy. Significant improvements were detected in the emotional and

social functionality and sleep quality of patients following the ketogenic diet compared to those following the standard diet. Compared to the standard diet group, it was stated that the increase in breast symptoms in the ketogenic diet group was less, and metabolic health markers (such as creatinine, triglycerides) improved significantly with the ketogenic diet (Klement et al., 2021). Women (age ≥ 19) with ovarian and endometrial cancer experienced selective fat mass loss after 12 weeks following the ketogenic diet. It has been stated that fasting serum insulin is reduced by the ketogenic diet. It has been suggested that elevated serum β -hydroxybutyrate may create a metabolic environment unfavourable for cancer proliferation (Cohen et al., 2018).

Side effects and possible health risks of ketogenic diet

In addition to the positive effect of the ketogenic diet on weight loss, studies have shown that the diet significantly reduces serum triglycerides (Shah and Mohan, 2015). A decrease in total cholesterol and an increase in HDL (high density lipoprotein) levels have been noted. There is 3-hydroxy-3-methylglutaryl-CoA reductase enzyme, which is activated by insulin, in cholesterol biosynthesis. Thanks to this enzyme, the increase in blood glucose and subsequent insulin levels also increases the endogenous cholesterol level (Tony David et al., 2017; Shilpa and Mohan, 2018). A transient occurrence of endothelial dysfunction has been detected shortly after the start of the ketogenic diet, which may further worsen an already stressed atherosclerotic vascular system (Luong et al., 2022). Short-chain fatty acids are the products of fermentation in the intestine of indigestible foods such as dietary fiber. Thanks to lipid metabolism and glucose homeostasis, it has an improving effect on insulin sensitivity and general metabolic health.

However, since dietary fiber intake is limited during the ketogenic diet, it also reduces the production of short-chain fatty acids at the same rate (Hernández et al., 2019; Ferraris et al., 2021). The ketogenic diet also has side effects such as short-term constipation, headache, diarrhea, nausea, muscle cramps and fatigue, which are called 'keto flu' (O'Neill and Raggi, 2020). Apart from this, it has been stated that long-term effects may include hepatic steatosis, hypoproteinemia, hypocitraturia, hypercalciuria, kidney stones, risk of heart attack, vitamin and mineral deficiencies (Masood et al., 2023).

Conclusion

There is evidence that the ketogenic diet may address various health problems through different mechanisms of action. Ketogenic diet causes significant changes due to increased fatty acid oxidation and decreased glucose flux, which may be an effective mechanism for cancer treatment. The ketogenic diet can have an anti-tumor effect by targeting tumor metabolism, inflammatory process and gene transcription. From the presented studies, it has been supported that the diet provides a beneficial effect as an adjuvant treatment in mice and humans when applied together with other methods. As a result, the ketogenic diet appears to be a promising and powerful option for cancer treatment. More randomized controlled trials are needed to apply it as a standard protocol on cancer.

Conflicts of Interest

The authors declare no conflicts of interest.

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