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Review Article

From weight loss to cancer treatment: Fasting as an adjuvant anticancer therapy

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Abstract

The number of studies that have been conducted on the possible benefits of different types of fasting or calorie restriction on cancer therapy, including the likelihood that these treatments lessen side effects, has been limited. However, the results are nevertheless promising.

Chemotherapy's adverse effects have led to a quest for options that reduce reliance on it. The susceptibility of tumorous cells to specific metabolites and nutrient deficiency is increasingly recognized as a key characteristic of the disease.

This review delves into the data on various fasting methods and calorie restriction in rodents and humans, with a focus on biological adaptations that could potentially lower cancer risk or enhance cancer treatment results. We also emphasize recent scientific developments regarding the use of prolonged fasting and fasting-mimicking diets as a possible additional treatment for patients receiving immunotherapy or other treatments. This approach shows promise in enhancing treatment effectiveness, preventing resistance, and minimizing side effects.

This study proposes that combining fasting and calorie restriction with chemotherapy, immunotherapy, or other therapies might be a potential technique to improve treatment efficacy, avoid resistance, and reduce adverse effects.

Keywords

cancer metabolism, glucose, Warburg effect

Introduction

The risk of having cancer is significantly influenced by dietary and lifestyle variables, with some malignancies being more reliant on dietary patterns than others (Lanier et al. 1976). It is estimated that between 14 and 20% of all fatalities in the United States that are attributed to cancer are caused by obesity (Calle et al. 2003). As a result, suggestions have been made to alter one's diet and increase one's level of physical activity in order to reduce the risk of developing

cancer (Kushi et al. 2012). When fasting, healthy cells slow down their division and become more resistant to toxic shocks from anticancer drugs, while making cancer cells more vulnerable to these treatments (Caffa et al. 2015). When fasting, metabolic pathways are affected, leading to a shift towards producing energy as well as metabolites from carbohydrates from adipose tissue (Lee et al. 2012). Alterations in hormone and metabolite levels lead to a decrease in cell proliferation and metabolic activity in healthy cells, ultimately shielding them from chemotherapy attacks (Raffaghello et al. 2008). Cells that resist the anti-growth signals under starvation conditions may react differently than normal cells, making them vulnerable to chemotherapy and other cancer treatments (Raffaghello et al. 2008).

The levels of glucose, insulin, glucagon, growth hormone (GH), insulin-like growth factor 1 (IGF1), glucocorticoids, and adrenaline that are circulating in the body contribute to the coordination of the fasting response. Insulin levels begin to decrease during the early post-absorptive phase, which typically lasts between six and twenty-four hours. At the same time, glucagon levels begin to increase, which stimulates the breakdown of liver glycogen stores (which are exhausted after around twenty-four hours) and the consequent release of glucose for energy (Pelt 2010). Adipose tissue produces glycerol and free fatty acids by breaking triglycerides. This response is produced by low insulin concentrations in the blood and by the simultaneous presence of glucagon. While certain bodily systems rely on fat stores for sustaining energy levels during fasting, the brain uses liver-produced glucose along with ketone bodies (Pelt 2010).

Fasting protects healthy cells from damage, an effect that has persisted through evolution and which has been shown to increase life expectancy and health span in experimental animals (Wei et al. 2008). The IGF1 pathway is a key signaling mechanism involved in the cellular mediation of fasting effects (van der Horst et al. 2007). Protein ingestion and increasing amino acid levels enhance IGF1 levels and promote the cellular activity of AKT and mTOR, resulting in increased translation of proteins (Cheng et al. 2009). While fasting, decreased levels of IGF1 and downstream signaling enable mammalian FOXO transcription factors to activate genes and trigger antioxidant enzymes including superoxide dismutase (SOD), catalase, and Haem oxygenase 1 (HO1) (Converso et al. 2006).

This study examined how fasting affects the development and management of cancer. The studies reviewed provide researchers with a thorough understanding of the molecular foundations of fasting's impact on cancer.

Fasting and cancer overview

Cancer is a disorder characterized by the uncontrolled growth of certain cells in the body with the ability to metastasize to other parts of the body. Anywhere in the body can be the starting point for this illness, and either malignant or benign (non-cancerous) cells might proliferate there. Unlike malignant tumors, benign tumors do not penetrate or spread to surrounding tissues (Vajihinejad 2022).

Research on the impact of fasting on cancer cells has increased due to cancer cells being sensitive to nutritional restriction and relying on certain metabolites and hormones. It is important to consider whether fasting in any of its forms might prevent or postpone the development of cancer.

Studies on chronic caloric restriction without malnutrition and short-term fasting (STF) for less than 24 hours revealed that these treatments play significant therapeutic roles in preventing the toxicity of chemotherapy and radiotherapy on normal tissues and halting tumor growth and metastasis in non-human primates. (de Groot et al. 2019).

As a result, research on long-term calorie-restricted human participants has unexpectedly demonstrated a decrease in hormonal and metabolic markers linked to cancer risk. Because chronic calorie restriction causes unacceptable weight loss and takes a long time to demonstrate results, it is not a clinically viable intervention. Extensive preclinical studies have shown that short fasting enhances the efficacy of chemotherapeutic medications in the treatment of many types of malignancies, such as pancreatic, breast, and melanoma. However, because STF strengthens the stress resistance of healthy cells, it has demonstrated its capacity to protest against the damaging effects of chemotherapy. When healthy cells are deprived of nutrients, they spend more energy on maintenance and repair, which makes them more resistant to chemotherapy. Therefore, chemotherapy induces apoptosis and increases DNA damage in tumor cells while sparing healthy cells when used in conjunction with short-term fasting (de Groot et al. 2019).

In contrast to numerous cancer therapies, brief fasting typically leads to mild and manageable side effects such as weakness, nausea, and headache. Furthermore, fasting is an affordable and convenient approach that demonstrates potential for effectively treating a wide variety of cancers (de Groot et al. 2019). Oncology-related dietary approaches are shown in Table 1.

Fasting and warburg effect on cancer

The oxidation of carbon bonds during glucose metabolism enables the capture of energy in the form of ATP. The foundation for maintaining all mammalian life is this procedure. The oxidative phosphorylation and the citric acid cycle are not the strategies that cancer cells solely use to generate energy; oncologists have noticed that cancer cells make energy in a manner that is distinct from that of healthy cells. Cancer cells generate energy via a process known as anaerobic glycolysis. To maintain their high rates of cellular proliferation, these cells mostly depend on glucose. The Warburg effect makes this apparent. The Warburg effect supports the tumor microenvironment, promoting the tumor cells' growth. Nevertheless, the Warburg effect offers signaling functions to tumor cells. Thorough investigation into the Warburg effect in cancer cells has increased our understanding of the elements that support tumor cell growth. Exploring nutritional and pharmacological treatments could enhance our understanding of the Warburg effect (Liberti et al. 2016).

Table 1. Oncology-related dietary approaches.

Type of diet	Description	Schedule	IGF1 reduction	Glucose reduction	Ketone bodies increase	Protection from chemotherapy toxicity	References
Fasting or FMD	A calorie-restricted, low-serum, low-glucose, low-carbohydrate diet	2–5 consecutive days/month	Yes	Yes	Yes	Yes (It has the potential to prevent chemotherapy-induced adverse effects and DNA damage in healthy cells).	(Nencioni et al. 2018), (Vernieri et al. 2020)
Intermittent fasting	Alternate periods of fasting and free feeding/eating.	Chronic	Yes	Yes	Yes	Yes (healthy cells are prompted to adopt a sluggish division and a well-protected phase, which shields them from damaging shocks created by anticancer medications).	(Nencioni et al. 2018), (Zhao et al. 2021)
Ketogenic diet	Regulated calorie intake	Chronic	Yes	No	Yes	NA	(Lee et al. 2012)
Calorie restriction	Vitamins and minerals. No other dierty constituent	Chronic	Only in the presence of protein restriction	No	No	Yes	(Brandhorst et al. 2013)

Healthy cells may adjust to lack of nutrients during brief fasting periods by transitioning from using glucose to utilizing fatty acids and ketone bodies for energy. However, short-term fasting up-regulates oxidative phosphorylation while down-regulates anaerobic glycolysis; thus, "the anti-Warburg effect" results in apoptosis and oxidative stress of tumor cells (Fig. 1). Decreased nutrition availability and lower glucose levels during short-term fasting may make tumor cells more susceptible to challenges like chemotherapy (de Groot et al. 2019).

Effects of fasting on hormone and glucose levels

Although the necessity of food for humans is crucial, fasting is suggested to enhance the organism's survival that is capable of enduring harsh or challenging conditions such as food scarcity, extreme temperatures, and UV radiation. Similarly, studies have proposed fasting as a way to decrease the toxic influence of chemotherapy (Deligiorgi et al. 2020).

Growth factors and hormonal changes influence gene regulation, affecting cell processes such as proliferation, differentiation, and DNA repair, leading to increased food consumption. This promotes cellular growth and survival despite the presence of cancer-causing mutations. Restricting food intake and nutrition significantly affects hormone levels and growth factors, eventually lowering the risk of cancer (Salvadori et al. 2021a).

During short-term fasting, serum glucose levels decrease, while glucagon promotes the creation of glucose inside the body. After twenty-four hours, glycogen reserves are exhausted. At this point, the brain is supplied with the required glucose for energy by gluconeogenesis, and fatty acids become the major energy source for the rest of the body. Ketone bodies are then formed by oxidation of fatty acids (Vajihinejad 2022).

Insulin levels drop significantly after 36–72 hours, leading to a fast reduction in Insulin-like Growth Factor 1 (IGF-1) synthesis. IGF-1 concentrations are strongly correlated with the high probability of developing several forms of cancer. Growth hormone (GH) stimulates the

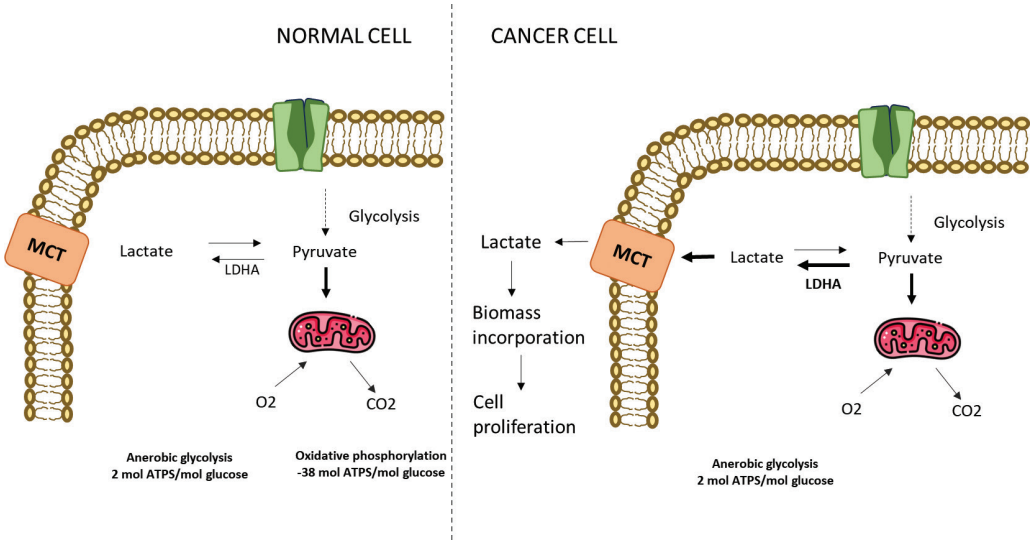

Figure 1. Metabolic differences between normal and cancer cells.

action of IGF-1 from the liver once it is released into the circulation. Due to prolonged fasting, the liver loses its sensitivity towards GH; thus, IGF-1 is reduced. Because of decreased circulating insulin and IGF, negative feedback is diminished, which leads to increased plasma GH levels. (Vajihinejad 2022) Lower IGF-1 levels lead to the reduction of the Ras/MAPK and PI3K/Akt pathways, preventing cell death and encouraging cell proliferation (Fig. 2). To maximize therapeutic advantages, it is advised to prolong the length of short-term fasting. As a result, a condition is created that limits the potential of tumor cells to adapt to the new condition and grow. Therefore, improving the effectiveness of cancer treatment (Vajihinejad 2022).

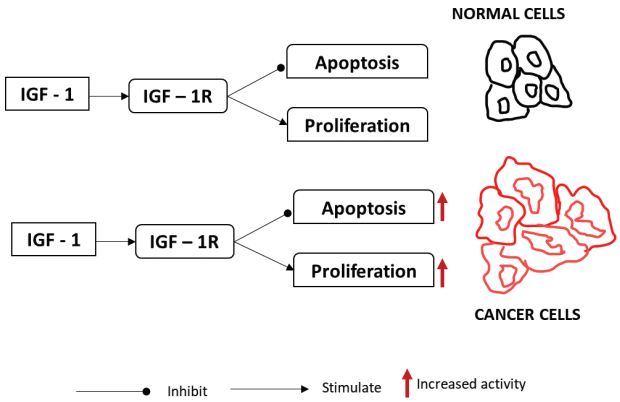

Figure 2. How IGF-1 plasma levels affect the proliferation and apoptosis of normal and cancer cells.

Fasting and fast mimicking diet (FMD) in cancer therapy

FMD stands for a diet that restricts calories and is low in glucose and carbohydrates. Cancer cells are increasingly being recognized for their vulnerability to lack of nutrients and reliance on certain metabolites. Fasting or fast-like diets (FMDs) induce notable alterations in growth factor and metabolite levels, hindering cancer cells' ability to adapt and survive while enhancing the efficacy of cancer therapy. Fasting or FMDs enhance chemotherapy resistance in normal cells without affecting cancer cells. They also speed up tissue regeneration in normal tissues, possibly reducing detrimental treatment side effects (Nencioni et al. 2018).

When paired with chemotherapy, hormone therapy, or another anticancer therapy, FMD can slow the growth of tumors in mice with tumors. It can also guard against induced toxicity in normal tissues (Vernieri et al. 2020). Reductions in insulin-like growth factor 1 (IGF-1), blood sugar, and insulin can be primarily brought on by these actions. The FMD is beneficial in reducing chemotherapy-induced toxicities in HER2 (human epidermal growth factor receptor) patients, according to preclinical evidence. Additionally, patients with early-stage BC who had a lower risk of malnutrition and cachexia participated in the study. The study conducted was a randomized trial that showcased the therapeutic advantages of FMD in a specific group of cancer patients, with significant statistical power (Vernieri et al. 2020).

In the DIRECT study, patients with FMD did not receive dexamethasone before doxorubicin-cyclophosphamide (AC) ChT. However, they did not have a higher rate of adverse events compared to patients in the control group. These statistics suggest that FMD may help prevent patients from experiencing various ChT-related complications such as nausea and vomiting, eliminating the need for dexamethasone premedication. Within certain therapeutic environments, the exclusion of dexamethasone administration could potentially enhance the anticancer effects of chemotherapy (Di Biase et al. 2016).

Two cycles of fasting/FMD improve antitumor immunity and facilitate the penetration of CD8+ T cells into tumors in preclinical in vivo trials by lowering blood IGF-1 levels, a crucial marker of the anticancer advantages of calorie restriction (Vernieri et al. 2020). It has been shown that consuming a reasonable amount of protein, particularly from plant-based sources, may have positive effects on the process of aging well up to the age of 65. The practice of intermittent fasting, also known as FMD, has gained popularity in recent years due to the fact that it is risk-free, simple to implement, and successful in lowering risk factors associated with aging, diabetes, cardiovascular disease, and cancer (Brandhorst et al. 2019).

Both the development of mammospheres and their volume were decreased in the in vitro human TNBC SUM159 model when fasting and FMD-mimicking conditions were applied. These circumstances, which are also known as short-term starvation (STS), include low serum and low glucose levels. FMD cycles dramatically slowed the development of the tumor, decreased the size of the tumor, and elevated the expression of Caspase3 internal to the tumor, which is indicative of apoptotic activation (Salvadori et al. 2021b).

Preclinical studies have demonstrated that STF could reduce the toxicity of various chemotherapeutic drugs and enhance their efficacy. A recent study found that STF can boost the impact of radiation based on preclinical investigations. In the clinical research field, FMD has demonstrated great potential in improving the efficacy and acceptance of chemotherapy. This can lead to unwanted side effects caused by chemotherapy and harm healthy cells by damaging their DNA (de Groot et al. 2019). An investigation was carried out on twenty patients who were observed during three different fasting periods (24, 48, and 72 hours). Fasting has been demonstrated to be safe and feasible for cancer patients. This study found initial signs of reduced DNA damage in host leukocytes following chemotherapy exposure among participants who fasted for 72 hours compared to 24 hours (Bauersfeld et al. 2018).

Clinical trials

Data on 24-hour dietary recall were collected from 2413 women with breast cancer who were between the ages of 27 and 70 and had no previous history of diabetes as part of general population research. Further investigation found that fasting for more than 13 hours per night was associated with a 36% decreased risk of breast cancer

recurrence compared to fasting for less than 13 hours per night (hazard ratio, 1.36; 95% confidence interval, 1.05–1.76). This was the conclusion reached when the data were discussed in further detail (Yuan et al. 2018).

Fasting-mimicking diets, or FMDs, were created to address the safety concerns associated with intermittent fasting. These problems include low rates of compliance and malnourishment. It was suggested that consuming fasting meals with low protein content, high healthy fats, and complex carbohydrates might be used as a short-term therapeutic program. It mimics the effects of fasting by decreasing activation of the insulin/glucose signaling pathway without leading to potential negative effects from essential nutritional deficiency (Safdie et al. 2009). Several preclinical studies highlight the advantages of combining FMDs with chemotherapeutic drugs, but only a few clinical trials on FMDs in patients receiving chemotherapy have been released (Caffa et al. 2020). A pilot clinical study was conducted with healthy persons to investigate the practicality of the FMD in humans as well as the possible consequences it may have. After that, a clinical crossover research study that was randomized was carried out where one hundred healthy individuals participated (Wei et al. 2017) (Brandhorst et al. 2015). A decline in body weight, a reduction in blood pressure, and a decrease in levels of IGF-1 and C-reactive protein were all produced as a result of the FMD (Levine et al. 2014). There is no established threshold for blood IGF-1 levels that indicates a clinically significant hazard. Multiple epidemiological studies have shown a link between high levels of IGF-1 (exceeding 200 ng/mL) and a higher likelihood of developing various types of cancer. The decrease in IGF-1 levels was almost four times more significant in those whose initial levels were below 225 ng/mL compared to those with higher baseline values (Pollak 2007).

During the fasting metabolic diet (FMD), patients were instructed to consume less than 400 kcal of vegetable juice daily, as well as certain quantities of light vegetable broth, beginning 36–48 hours before chemotherapy and continuing until 24 hours following treatment. Not only did FMD reduce fatigue, but it also avoided the decline in quality of life that was brought on by chemotherapy. This was accomplished without causing any major adverse effect (Pollak 2007).

In a study including 36 patients with hormone-receptor-positive/HER2 breast cancer, the combination of FMD with endocrine treatments has shown promising results. A total of ten cycles of FMD were administered to one patient during the course of the second-line therapy scenario, while two patients got eight cycles of the treatment (Rangan et al. 2019). By July 2020, two individuals had symptoms of a condition that was clinically controlled, while one patient saw disease progression after 11 months and eight cycles of FMD treatment; the median progression-free survival in this context is nine months (Safdie et al. 2009). During the clinical trials, the fasting metabolic diet (FMD) resulted in a decrease in serum levels of blood glucose, insulin-like growth factor-1 (IGF-1), and C-peptide, while simultaneously leading to an increase in the amount of ketone bodies in the blood. In accordance with the molecular insights obtained from preclinical research, these results are consistent.

Fasting mechanisms of action

Complete dietary restriction causes dramatic changes in the pro-growth signaling that is triggered by glucose and other foods in a number of different species. This results in metabolic reprogramming and an increased allocation of resources to defensive mechanisms (Di Biase et al. 2016).

It has been shown that these modifications may extend the lifetime of an individual and accelerate the regeneration of cells in a number of different systems, including the brain and hematological systems (Di Biase and Longo 2016). In conjunction with chemotherapy and radiation therapy, dexamethasone (Dexa), aprepitant, and lorazepam are frequently administered to enhance the efficacy of cancer treatments and manage complications associated with treatment. In addition to palliative care, the corticosteroid dexamethasone may also be utilized in the treatment of lymphoma, leukemia, and multiple myeloma. Research has indicated that Dexa therapy has the potential to cause an increase in blood glucose levels as well as an increased risk of cerebral injury (Di Biase et al. 2017).

Prior research has shown that giving mice STS (short-term deprivation) after exposing them to lethal dosages of DXR decreases mortality. C57BL/6 mice were given various doses of DXR STS for 48 hours to investigate whether the preventive effects of STS include reducing DXR-induced heart damage. The treatment dosage and timing were determined to provide extended exposure to DXR across many cycles when matching clinical doses and regimens. Current data suggests that short calorie restriction (SCR) might be a helpful additional dietary approach. However, because of the inconsistent and insufficient evidence, treatment recommendations do not officially endorse SCR. Most studies on the safety and effectiveness of SCR in cancer patients have used a diverse group of individuals, making it difficult to analyze the precise effects of SCR (Tang et al. 2021).

Intermittent fasting (IF) uses dietary interventions that involve alternate periods of fasting and free feeding/eating. Using IF helps to maintain a calorie-restricted program that is relatively safe and can be maintained over a lifespan (Zhao et al. 2021). The practice of intermittent fasting (IF) has been shown in a number of studies to have the potential to promote body as well as tissue and organ function improvement (Zhao et al. 2021).

Furthermore, after an IF regimen, various tissues and organs become more resistant to a range of damaging stimuli, such as oxidative, proteotoxic stressors, traumatic, metabolic, and ionic (Longo et al. 2014).

Disease studies on animals have also revealed that IF has the potential to slow down the progression of several chronic diseases, including obesity, cancer, diabetes, neurodegenerative disorder, and vascular diseases (Di Francesco et al. 2018).

Ketone levels, autophagy, and DNA repair are all increased during the first stages of intermittent fasting. There is an increase in stress resistance, antioxidant defenses, glucose production, intracellular protein synthesis, and mitochondrial biogenesis when it is present during periods of recovery such as eating and sleeping. The process of long-term adaptation improves blood glucose homeostasis and lipid metabolism, as well as lowers abdominal obesity and inflammation. It also increases the sensitivity of cells to insulin and the body's resistance to insulin (Karbowska et al. 2012; Harvie et al. 2013; Arum et al. 2014; Gotthardt et al. 2016).

Considered one of the central regulatory regions, the hypothalamus responds immediately to peripheral impulses. IF influences the hypothalamus by increasing CRH and TRH levels, which regulate energy homeostasis, thereby reducing food intake and appetite during fasting (Cantó et al. 2010).

Calorie restriction induced by IF inhibits the IGF-1/AKT and mTORC1 pathways in tumor cells, whereas activation of AMP-activated protein kinase (AMPK), which is dependent on the nicotinamide adenine dinucleotide coenzyme deacetylase-1 (Sirtuin-1, SIRT1) and SIRT3 pathways, enables the inhibition of tumor cell proliferation. AMPK and SIRTs are reciprocally dependent on metabolic adaptation associated with IF (Cantó et al. 2010; Silvestre et al. 2014).

SIRT1 has the ability to activate AMPK via liver kinase B1 (LKB1), while AMPK has the potential to activate SIRT1 through nicotinamide phosphoribosyltransferase (NAMPT as well). Additionally, FOXO3a, which is a protein that belongs to the downstream of SIRT1 and SIRT3, and AMPK are both capable of promoting the transcriptional activity of the other (An et al. 2020).

SIRT3 suppresses tumor growth by stimulating FOXO3a and enhancing SOD2 levels, leading to a reduction in reactive oxygen species (ROS) levels (Qiu et al. 2010; Tao et al. 2010; Torrens-Mas et al. 2020). In addition to inhibiting the expression of genes that are stimulated by oxygen. SIRT3, an HIF-1 (hepatocyte growth factor-1), increases the expression of FOXO3a, thereby stimulating SOD2 (Sundaresan et al. 2009; Finley et al. 2011; Kenny et al. 2017).

Recent research has shown that IF may alter tumor cell energy metabolism, reduce tumor cell proliferation, increase immune cell function, and boost anti-tumor immune responses, hinting that IF might be effective in tumor immunotherapy (Zhao et al. 2021). Fasting leads healthy cells to enter a slow division and highly protected phase, shielding them from harmful shocks caused by anticancer drugs while making cancer cells more susceptible to these therapies. This discovery implies that a single dietary intervention may be used to address many equally critical aspects of cancer therapy. In this opinion article, they discuss the biological rationale for using fasting or fasting mimicking diets (FMDs) to not only lower TEAEs but also to prevent and cure cancer (Nencioni et al. 2018).

Although research on the impact of intermittent fasting (IF) in nonhuman primates is limited, clinical studies have been conducted to investigate its potential in controlling metabolic and hormonal factors related to cancer development or outcome. Trials have mostly included non-cancer patients, since different formulations of intermittent fasting have shown feasibility and a positive impact on weight reduction in overweight and obese individuals (Clifton et al. 2021). ADF or 5:2 diets enhance a range of cancer risk factors, including increased adiponectin 130 and lower fasting glucose, insulin, and leptin levels, all of which have been associated with cancer development, according to various short-term (2–6 months) randomized clinical studies. Several 12-month IF studies, on the other hand, failed to show significant increases in insulin sensitivity or CRP levels (Clifton et al. 2021).

Effects on immune system

The ability to evade the immune system is essential to the development of cancer. IF has been shown to have an effect on the formation and functioning of a variety of immune cells, which in turn regulates antitumor immune responses and has an effect on the growth of cancer, according to research.

Interferon modulates antitumor immunity by enhancing the self-renewal ability of hematopoietic stem cells and enhancing immunosuppression. Moreover, the alteration in energy metabolism led to a significant reduction in IGF-1 and an increase in insulin-like growth factor-binding protein (Lu et al. 2017), along with increased tumor cell autophagy and programmed cell death. The consequences include decreased extracellular nucleoside triphosphate diphosphohydrolase expression and ATP accumulation, leading to the inhibition of regulatory T cells (Tregs) and an increase in cytotoxic T lymphocyte (CTL) activities, hence enhancing anticancer immune responses (Fontana et al. 2008).

Moreover, elevated production of Heme oxygenase-1 (HO-1) in malignancies has the potential to inhibit the demise of tumor cells and inhibit immune-stimulatory effects. (Ko et al. 2014) Intermittent fasting (IF) may boost the activation of CD8+ T cells and reduce HO-1 expression in tumor cells by limiting calorie intake. This process leads to increased tumor cell death via CD8+ T cell activity, creating a beneficial cycle of tumor cell elimination produced by IF (Liu et al. 2004).

IF has the potential to influence immune responses against cancer by modulating the activity of immune cells, including tumor-associated macrophages (TAMs) and natural killer (NK) cells (Englert et al. 2016). Intermittent fasting may enhance the body's repair and immunological monitoring by stimulating AMPK and decrease the metabolic and inflammatory functions of monocytes via activation of the peroxisome proliferator-activated receptor (PPAR), respectively. Blocked production of the chemokine C-C motif ligand 2 further reduces the number of monocytes associated with inflammation in the circulation and tissues during IF (Husain et al. 2013).

Combined effect with chemotherapy

A number of yeast oncogene orthologues, including Ras and Sch9 (which is the functional orthologue of human S6K), have the ability to decrease the organism's tolerance

to stress in experimentation (Jordan et al. 2019). Additionally, mutations that activate IGF1R, RAS, PI3KCA, or AKT, or mutations that inactivate PTEN, are seen in the great majority of breast cancers and other forms of human cancer (Fabrizio et al. 2001). This concept posits that hunger might exert an opposing influence on cancer cells, impeding their capacity to endure cellular stresses such as chemotherapy in comparison to healthy cells. Hypoxia during the lifespan of healthy cells may result in an imbalance in stress resistance (DSR) between healthy and malignant cells. As per the DSR hypothesis, in response to starvation, healthy cells decrease the activity of genes associated with ribosome synthesis and cell growth. This mechanism enables cells to enter a state of self-maintenance, thereby safeguarding them against detrimental effects induced by treatments such as radiation and chemotherapy. Cancer cells undergo restricted self-maintenance as a result of oncogenic modifications that promote the ongoing suppression of stress response pathways. (Hanahan et al. 2011).

S. cerevisiae cells resistant to oxidative stress or chemotherapy showed a 100-fold increase in resistance to short-term fasting or deletion of proto-oncogene homologs (Sch9, both Sch9 and Ras2) compared to yeast cells containing the constitutively active oncogene homolog Ras2val19. Primary mouse glia cells were protected against damage caused by hydrogen peroxide or cyclophosphamide when cultured in a low-glucose medium. It did not provide equivalent protection for glioma and neuroblastoma cancer cell lines from mice, rats, or humans. Research results indicate that a two-day fast improved the survival rates of mice receiving high-dose etoposide and mice with neuroblastoma allografts compared to their non-fasted counterparts (Hanahan and Weinberg 2011). It has been shown that cycles of fasting may boost bone marrow regeneration, inhibit cyclophosphamide-induced immunosuppression via PKA and IGF1 pathways, lessen the damage that chemotherapy causes to cells, and increase survival rates in mice that have been treated with chemotherapy (Raffaghello et al. 2008). Fasting and FMDs have the potential to boost chemotherapy tolerance and minimize significant adverse effects, according to promising preclinical studies.

The antitumor effect of fasting is attributed to reductions in IGF1 and glucose levels, which may help distinguish the impact of anticancer therapy on benign cells from malignant ones. This technology will inhibit the growth of several types of cancerous cells, such as solid tumor cell lines, lymphoid cells, and murine leukemia cells. The main goal is to make cancer cells more responsive to tyrosine kinase inhibitors, chemotherapy, and radiation (Raffaghello et al. 2008).

Ketogenic diet and FMD

A diet that is low in carbs and high in fat is known as the ketogenic diet (KD), which is a calorie-controlled diet (Lee et al. 2012). It is possible that the ketogenic diet will cause a significant increase in the amount of circulating ketone bodies (0.5 mmol per liter). In humans, a ketogenic diet has the potential to reduce insulin and IGF1 levels by more than twenty percent from their original values. However, the amount and kind of carbs and proteins that are consumed may have an impact on the potential consequences of this diet (Oliveira et al. 2018). The ketogenic diet has the potential to maintain blood glucose levels within the normal range, which is defined as being more than 4.4 mmol per liter (Oliveira et al. 2018). Additionally, it may be used to prevent high amounts of glucose and insulin (Urbain et al. 2017).

In the event of glucose deprivation, the body recognizes the necessity to generate an alternative form of energy for cellular functioning. Ketones and fatty acids produced by the liver are beneficial to healthy cells but not to malignant cells. The malfunctioning mitochondria and possible disruptions in the electron transport chain of cancer cells impede the regular synthesis of mitochondrial adenosine triphosphate (Hopkins et al. 2018). On account of this, cancer cells develop an excessive dependence on ATP produced via the less efficient glycolysis pathway. Ketogenic diets aim to replicate the physiological state of fasting, wherein the body generates ketones as an alternative energy source in response to a glucose deficiency. As defective mitochondrial oxidative phosphorylation induces deficiencies in ATP production that are compensated for by excess lactate production as part of the Warburg effect [68], the resulting tumor glucose dependence can be exploited with KD. Ketogenic diets selectively deprive cancer cells by providing them with fat and protein, both of which are indigestible by glucose-dependent tumor cells (Tian et al. 2004). Enzymes affected by a ketogenic diet are shown in Table 2.

The low-carbohydrate modified Atkins KD diet, which consists of < 20 grams of carbohydrates per day, was subjected to a feasibility trial for a duration of four weeks, conducted on PET-positive advanced cancer patients who had solid tumors. There was a correlation between insulin levels and ketosis, but not with IGF. A threefold rise in ketosis was seen in patients who were in a stable illness or partial remission, in comparison to patients who were experiencing progression of their condition. This occurred without any substantial changes in weight loss or calorie intake (Ho et al. 2011).

Twenty patients with recurrent glioblastoma who were receiving KD supplemented with plant oils were the subjects of the ERGO research, which was conducted by Rieger and colleagues (Fine et al. 2012). There were no calorie restrictions whatsoever. The proportion of patients who were able to successfully discontinue the diet was the primary outcome. Although there was a significant reduction in the average weight, there was no improvement in the quality of life (QOL). Using a mouse model of glioblastoma, the researchers also studied the effects of KD either on its own or in conjunction with bevacizumab. Although KD did not have any effect on the protest of the mice in this experiment, when it was paired with bevacizumab, it increased the median survival time from 52 to 58 days.

Table 2. Enzymes affected by ketogenic diet.

Enzyme name	Description	Role in carcinogenesis	Effect of ketogenic diet on enzyme	Reference
Matrix metalloproteinases (MMPs)	class of zinc-dependent endopeptidases that are important enzymes in the degradation of the extracellular matrix.	Numerous MMPs are involved in cancer development, migration, invasion, metastasis, and angiogenesis.	Significant decrease in MMP-9 expression in several kinds of cancer.	Rieger et al. 2014; Mondal et al. 2020
Pyruvate kinase (PK)	terminal glycolytic enzyme that catalyzes ATP and pyruvate synthesis by converting phosphoenolpyruvate (PED) to adenosine diphosphate (ADP).	Pyruvate kinase M2 (PKM2) is the most abundant isoform involved in cancer cells and plays an important role in cancer metabolism.	KD inhibited the expression of PKM2, lowering glucose absorption and lactate formation in tumor cells, hence destroying the Warburg effect, which is thought to be a survival technique for cancer cells.	Tan et al. 2020
P53	Transcription factor in the nucleus that functions as a tumor suppressor factor.	It is involved in controlling cell proliferation, apoptosis, and genetic stability.	KD either prevents or silences p53 mutant function during malignant initiation and development.	Levine et al. 2009; Li et al. 2020
AMP-activated protein kinase (AMPK)	serine/threonine protein kinase found in a variety of cells.	AMPK plays a critical role in cancer prevention.	Glucose replacement with ketone bodies in cancerous cells.	Motoshima et al. 2006; Umezawa et al. 2017

Ketogenic diet and Matrix Metalloproteinases (MMPs)

A class of zinc-dependent endopeptidases, also referred to as matrix metalloproteinases (MMPs), functions to contribute to the breakdown of extracellular matrix (ECM). This process is vital to establish and maintain cell integrity and, hence, the three-dimensional body structure (Rieger et al. 2014). Moreover, several MMPs have a role in cancer progression by breaking down extracellular matrix proteins and contributing to processes such as migration, invasion, metastasis, and angiogenesis (Laronha et al. 2020). Several types of cancer, including colorectal cancer, glioma, and gastric cancer, have been shown to have elevated levels of MMP-1, 2, 3, 7, 9, and 13 (Sampieri et al. 2010; Said et al. 2014; Woolf et al. 2015). MMP-9 is a member of the gelatinase subfamily of matrix metalloproteinases (MMPs) and is mostly generated by cancer cells, stromal cells that are located close to a tumor, and inflammatory cells (Mondal et al. 2020). When combined with other conventional cancer treatments, the implementation of a ketogenic diet is expected to result in a large reduction in the expression of MMP-9 in a number of different types of cancer (Zhang et al. 2020).

Ketogenic diet and pyruvate kinase

The terminal glycolytic enzyme pyruvate kinase catalyzes the generation of ATP and pyruvate by changing phosphoenolpyruvate (PED) into adenosine diphosphate (ADP) (Zhang et al. 2020). The most prevalent of the four encoded PK isoforms, pyruvate kinase M2 (PKM2), is crucial for the metabolism of cancer cells. (Wong et al. 2015) In their study on colon cancer, Zhang and colleagues discovered that a ketogenic diet (KD) decreased the expression of PKM2, which in turn led to a decrease in the amount of glucose that was absorbed and the amount of lactate that was produced by tumor cells. Because of this, the Warburg effect, which is a survival strategy used by cancer cells, was eradicated (Zhang et al. 2020). Furthermore, PKM2 isoforms are important in carcinogenesis, cell proliferation, and hypoxia-inducible factor-1alpha (HIF-1alpha) activity (Wong et al. 2015).

Ketogenic diet lowers the transcription of P53

A transcription factor P53, localized in the nucleus, is responsible for regulating cell proliferation, apoptosis, and genetic stability, which allows it to reduce the risk of tumor development (Levine et al. 2009). The protein ligase MDM2 is responsible for the destruction of P53, which is produced in normal cells at a very low activity level (Ozaki et al. 2011). On the other hand, mutations in p53 are common in the vast majority of cancers (Courtnay et al. 2015). These mutations lead to the cytoplasmic accumulation of mutated proteins that have a longer half-life, which ultimately results in resistance to treatment (Freed-Pastor et al. 2012). KD has been demonstrated in several studies to play a significant part in the process of deacetylation, which is responsible for lowering the activity of mutant p53 and ultimately causing cell death (Weber et al. 2020). The lowering of mutant p53 expression lengthens life (Li et al. 2020). Furthermore, a diet that is low in glucose causes the deacetylation and degradation of p53 mutants, which in turn inhibits or suppresses the action of p53 mutants at the beginning stages of cancer and throughout its course (Liu et al. 2019).

Ketogenic diet influences the activation of AMP-Activated Protein Kinase (AMPK)

The serine/threonine protein kinase known as AMP-activated protein kinase (AMPK) may be found in different types of cells (Motoshima et al. 2006). Inhibition of AMPK has the potential to be used in the treatment of a wide range of malignancies, including lung, bowel, and liver cancer. (Li et al. 2015). The activation of AMPK is linked to the presence of tumor suppressor genes such as p53 and LKB1, which ultimately results in the suppression of cell proliferation, resistance to inflammation, decrease of cell growth, and arrest of the cell cycle. As a result, AMPK is an essential component in the process of avoiding cancer (Wang et al. 2016). Energy deficiency due to several factors, such as hypoxia or glucose deprivation,

leads to its activation (Lee et al. 2009). Furthermore, metformin, curcumin, quercetin, and certain nonsteroidal anti-inflammatory medications have been shown to activate AMPK (Umezawa et al. 2017).

Furthermore, the ketogenic diet intake also promotes the glucose uptake in cancer cells by ketone bodies, which is reported to have an association with increased activation of AMPK (Tan-Shalaby 2017).

Calorie restriction in cancer prevention

Providing that there is no starvation, calorie restriction (CR) is the physiological strategy that has been shown to be the most effective and reliable in extending the lifespan of animals and avoiding cancer (Hursting et al. 2003; Fontana et al. 2007). Moreschi stated that CR reduces the development of malignancies implanted in mice in 1909 (Moreschi 1909). Studies have shown that caloric restriction (CR), which involves consuming fewer calories than normal without causing starvation, prevents radiation-induced, chemically-induced, and spontaneous cancers in several animal models (Tannenbaum et al. 1949; Thompson et al. 2003). According to studies on different types of animals, cancer prevention or delay depends on type of cancer (Tannenbaum and Silverstone 1949; Cheney et al. 1983), CR initiation age, its intensity, and the animals' genetic background or strain (Tannenbaum and Silverstone 1949; Pugh et al. 1999; Thompson et al. 2003).

Mechanisms at which CR (calorie restriction) works.

Reduced anabolic hormone and growth factor production (Merry et al. 1981; Sonntag et al. 1999).

Diminished generation of reactive oxygen species, lower oxidative stress, and free radicals that caused damage to DNA (Youngman et al. 1992; Sohal et al. 1996).

Lowered plasma inflammatory cytokine levels and a rise in circulating ghrelin, corticosteroids, and adiponectin, resulting in inflammatory reduction (Matsuzaki et al. 2001; Grossmann et al. 2008).

Simultaneously, CR influences several pathways involved in cancer formation. These activities include accelerated DNA repair mechanisms, enhanced removal of damaged cells by apoptosis, better autophagy, and protection against many harmful agents such as genotoxic and toxic chemicals (Weraarchakul et al. 1989; Cuervo et al. 2005).

The benefits of CR include several different impacts, including the stimulation of genes that inhibit cancers, the support of DNA and cell repair, the regulation of protein turnover, the enhancement of stress tolerance, and the promotion of antioxidant activity. Additionally, it inhibits the activity of genes that are responsible for inflammation and has an impact on gene modulation, mostly via the regulation of gene expression. Calorie restriction strategies and methods (Dhahbi et al. 2004; Park et al. 2005).

Endocrine regulation of cancer by insulin-like signals

IGF-1, in conjunction with other anabolic hormones such as insulin and sex steroids, regulates the metabolism of energy, the development and specialization of cells, the size of the body, and the longevity of an individual dependent on the amount of calories and protein that they consume (Prisco et al. 1999; Flötotto et al. 2001; Yu et al. 2003). IGF-1 stimulates cell growth and prevents cell death in several types of cancer cells, resulting in a strong cell division-promoting impact (Prisco et al. 1999; Ramsey et al. 2002). Prolonged usage of caloric restriction will decrease blood IGF-1 levels, which may hinder cancer advancement and delay the aging process (Hursting et al. 1999; Sonntag et al. 1999; Colbert et al. 2003; Colbert et al. 2009). Glucocorticoid supplementation restores repression, and adrenalectomy restores the cancer-protective effects of corticosterone. Therefore, the rise in corticosterone mediated by CR may also significantly contribute to cancer prevention (Stewart et al. 2005).

Dwarf mice lacking growth hormone (GH) and insulin-like growth factor-I (IGF-I) experience weight increase in middle age and have a lifespan that is about 40% longer (Berryman et al. 2004). Nevertheless, these mice do not become obese and may live up to twice as long as wild-type and ad lib-fed mice under calorie restriction (Bartke et al. 2008).

Excess adiposity due to excessive calorie consumption and insufficient physical exercise increases the chance of getting cancer, according to data from experimental and epidemiological research. Calorie restriction without starvation and potentially protein restriction, on the other hand, prevent cancer.

Conclusion

Over the course of the last three decades, several studies have been carried out associating fasting with cancer treatment. The role of fasting as intermittent fasting, short-term fast mimicking diet, and other calorie deprivation methods showed a great impact on cancer on the molecular level and even showed significant potency as a therapeutic agent along with chemotherapy.

The anti-Warburg action caused tumor cells to undergo apoptosis and oxidative stress while also promoting cell proliferation.

Fasting may influence the capacity of the modified cancer cell to develop and invade while also reducing the frequency of oncogene mutations. Calorie restriction, the ketogenic diet, and intermittent fasting were dietary changes that demonstrated a significant impact on cancer prevention and also had a great deal of potential as therapeutic agents. The implemented dietary modifications led to several beneficial outcomes, including a reduction in the activation of pro-aging pathways, inflammation, and growth in precancerous and normal adjacent cells, and an increase in apoptosis in damaged

cells. Even though pinpointing every environmental and genetic element would provide us with a complete road map for the future in terms of lowering the incidence of cancer and improving treatment, there are still a lot of unresolved problems with this illness.

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