Diet-Based Interventions Against Cancer: Potential Adjuvants to Standard Cancer Therapy

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Abstract

Different diet-based approaches have been studied as potential adjuvants to standard cancer therapies in human clinical trials. However, these diets have been shown to have complications such as non-compliance and adverse side effects. This paper investigates four different types of diet-based approaches used in human clinical trials and compares their complications. The four diet-based approaches evaluated in this paper are ketogenic diet (KD), protein restriction, fasting and fasting mimicking diets (FMD), and combined interventions. Research shows that KDs have large reports of non-compliance from subjects, with subjects also experiencing significant weight loss, constipation, and fatigue. Protein restriction diets have greater levels of adherence from subjects but may lead to harmful hematological toxicities. Fasting and FMD showed greater adherence than subjects on KDs, and lower toxicities than subjects on protein restriction diets, but had a greater number of complaints of headaches, hunger, and dizziness. Finally, combined interventions have the fewest reports of side effects and non-compliance but suffer from a limited number of case studies. Given these results, diet-based interventions require further research to minimize side effects and non-compliance before becoming an accepted adjuvant to standard cancer therapy.

Keywords: diet-based therapy; complications; adjuvant; fasting; cancer intervention

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Caloric restriction and fasting have previously been shown to increase life span, reduce oxidative damage, and enhance stress resistance in animal and human studies (de Groot et al., 2015; Safdie et al., 2009). They have even been shown to delay and possibly prevent aging and age-related diseases such as cancer, cardiovascular disease, and neurodegenerative diseases like Parkinson's and Alzheimer's in mice, rats, and non-human primates (De Cabo & Mattson, 2019). In the last 15 years, some researchers have focused on the anticarcinogenic effects of diet-based approaches in human clinical trials. Diet-based therapies have been identified as a potential adjuvant to traditional cancer therapy—a treatment given in addition to traditional cancer therapies with the aim of increasing overall effectiveness and protecting against adverse side effects. However, there are clinical complications associated with diet-based therapies. The two main complications discussed here are non-compliance and adverse side effects. Non-compliance results from diets being non-palatable, restrictive, and too difficult to adhere to. Additionally, some of these diets result in adverse side effects including nausea, diarrhea, and hematological toxicities. Researchers are studying different types of diets to observe potential anticarcinogenic effects while minimizing complications. There are four different types of diets that have been studied in human clinical trials: ketogenic diet (KD), protein restriction, fasting and fasting mimicking diet (FMD), and combined interventions. This paper investigates the four diets' effectiveness as an adjuvant to cancer therapy and the resulting complications in order to make an appropriate recommendation. There are two reasons this paper focuses on the general relationship between diet-based interventions and cancer, rather than focusing on a specific tumor group: first, diet-based interventions utilize the metabolic pathway of cancer cells, making it an effective intervention across multiple cancer types; second, the current human clinical trials assess these interventions in a variety of patients with different cancer groups and types.

Ketogenic Diets

KDs have come to light in recent years as a potential adjuvant therapy for cancer (Cohen et al., 2018). The diet, which usually consists of a low-carbohydrate and high-fat profile, is effective in creating a metabolic disadvantage for cancer cells by shifting the body into a state of ketosis—a metabolic state where the primary fuel source is switched from glucose and carbohydrates to ketones and fat. Many cancer cells are dependent on glucose for fuel acquisition and are unable to metabolize ketone bodies (Shaw, 2006; Tan-Shalaby et al., 2016).

Zuccoli et al. (2010) presented a case report observing the regression of glioblastoma multiforme (GBM) in a 65-year-old woman who followed a KD while undergoing standard therapy (radiation with temozolomide chemotherapy). The observed level of regression of GBM within 2.5 months of the diet and standard therapy was not previously reported in patients using standard therapy alone. From the case report, the results suggest that a KD may potentially increase tumor cell vulnerability to standard radiation with chemotherapy, reduce inflammation, and reduce brain tumor growth by lowering overall circulating levels of glucose (Zuccoli et al., 2010).

In a randomized control trial examining KDs in the context of cancer, researchers tracked levels of physical functioning and energy in female patients with ovarian or endometrial cancer while following a 12-week KD (Cohen et al., 2018). When compared to non-KD control groups and relative baseline levels, women on the KD reported significantly higher physical functioning and improvements in energy levels (Cohen et al., 2018).

Maintaining a KD while undergoing standard cancer therapy, however, presented several challenges across multiple studies. In another study observing the effectiveness of a KD in improving therapeutic outcomes in patients with non-small cell lung cancer, most subjects were unable to follow the KD for the duration of clinical treatment due to the KD being too restrictive and unpalatable (Zarah et al., 2017). Other challenges of therapeutic KD's for cancer include significant

weight loss (up to 20% of original body weight), constipation, nausea, fatigue, hyperuricemia, and poor accrual and adherence (Anderson et al., 2016; Bannerman et al., 2014; Dardis et al., 2017; Zuccoli et al., 2010).

Protein restriction

Another option is the protein restriction approach. Several tumor cells are characterized by a high rate of growth and require specific proteins in order to proliferate and survive (Thivat et al., 2007). The amino-acid methionine (MET) has been identified as necessary for tumor cell growth as tumor cells lose their ability to proliferate in growth medium when MET is replaced by its immediate precursor, homocysteine, even though normal cells would grow in this medium (Thivat et al., 2007). Tumor cells' "MET dependency" may be a result of MET's wide range of functionality as it protects against oxidative stress, contributes to protein synthesis, nuclear and cell division, and provides the methyl groups for DNA methylation. (Durando et al., 2008). In theory, a diet with low or no MET would reduce mean plasma MET concentrations in the blood, subsequently limiting the overall supply of MET available to tumor cells and decreasing the tumor cells' overall survivability and replication efficacy (Durando et al., 2010).

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A MET-free diet in combination with standard cancer therapies has been studied in human clinical trials. Durando et al (2008) and Thivat et al (2009) presented a 2-phase clinical trial observing patients with recurrent glioma or metastatic melanoma treated with standard therapy (chloroethylnitrosoureas) and dietary MET restriction. These studies observed short-term disease stabilization, a downward regulation of O6-methylguanine-methyltransferase (MGMT) activity (which is associated with increased tumor cell sensitivity to chloroethylnitrosoureas), improved therapeutic index of chloroethylnitrosoureas, and multiple cases of long-duration disease stabilization. (Durando et al., 2008; Thivat et al., 2007, 2009). These studies also reported successful reduction rates of blood MET concentration in patients undergoing the diet, reporting reduction rates ranging from 40.7 to 53.1% (Durando et al., 2008; Thivat et al., 2007, 2009).

Durando et al. (2010) studied dietary MET restriction in patients with metastatic colorectal cancer undergoing standard chemotherapy. When compared to baseline levels, the study observed a successful decrease in plasma MET concentration and reported positive partial responses from several patients, one patient with long-term (13 months) disease stabilization, and one patient with complete remission after a 30-month follow-up (Durando et al., 2010).

Other clinical trials observed increased levels of leptin receptors and increased phosphorylation of tyrosine residues on the insulin receptor signal transducer protein IRS1, indicative of increased insulin sensitivity in prostate cancer patients following dietary protein restriction (Eitan et al., 2017). Increased sensitivity to leptin and insulin has been associated with inhibited tumor growth (Eitan et al., 2017).

These clinical trials all reported several challenges faced by patients undergoing the MET-free

diet. While maintaining a protein restricted diet, several patients experienced hematological toxicity including World Health Organization (WHO) Grade 3 thrombocytopenia, WHO Grade 3 neutropenia, and WHO Grade 3–4 leucopenia[1] (Durando et al., 2010; Thivat et al., 2009). When compared to control patients without dietary MET restriction, there were increased difficulties with constipation, diarrhea, nausea, or vomiting, and this resulted in a low acceptability of the MET-free diet by patients (Durando et al., 2010). Compliance was also an issue, with reports of diets not being palatable (Durando et al., 2010). Other side effects included catabolism of muscle proteins and undesired decreases in BMI as a result of the diet (Durando et al., 2010).

In addition to the numerous adverse side effects, significant anticarcinogenic results of the MET-free diet in clinical trials are still inconclusive. Reports of disease stabilization are limited and lack consistent evidence, with some studies even observing cases of disease progression (Durando et al., 2008, 2010; Thivat et al., 2009).

Fasting and Caloric Restriction

Fasting is another dietary approach that has been investigated for its anti-cancer therapeutic benefits. Fasting may involve abstinence from all food, shifting an individual's metabolism into a state of ketosis—an unfavorable growth environment for cancer cells that is similarly achieved by KDs (Cohen et al., 2018; Nencioni et al., 2018). Low glucose levels from fasting also results in the upregulation of certain stress resistance proteins, protecting normal cells against stress and toxic insults, including those derived from standard cancer treatments (Nencioni et al., 2018).

There are several studies investigating the effects of fasting and a FMD in combination with standard cancer therapies in human patients. Safdie et al. (2009) presented a case series report of 10 patients with a variety of malignancies who fasted for various hours prior to and/or following chemotherapy. The study observed general and substantial reductions in chemotherapy-induced side effects including fatigue, weakness, vomiting, and diarrhea in patients who fasted during treatment (Safdie et al., 2009). Patients who completed the diet protocol also self-reported it as well-tolerated (Safdie et al., 2009).

De Groot et al (2015) observed the protective effects of short-term fasting in female patients undergoing chemotherapy for breast cancer. Patients who fasted for 24 hours before and after chemotherapy treatments showed good tolerance of the diet, significantly higher mean erythrocyte and thrombocyte counts 7 days after chemotherapy (possibly indicating a decreased breakdown of circulating normal cells from treatment) and no difference in toxicities from the diet (de Groot et al., 2015). Compared to fasting patients, non-fasting patients showed a significantly higher level of chemotherapy-induced DNA damage in peripheral blood mononuclear cells at 30 minutes and at 7 days after chemotherapy, suggesting fasting may protect cells from toxicities, chemotherapy-induced DNA damage, and accelerate the recovery of damaged cells (de Groot et al., 2015).

Similarly, Dorff et al. (2016) observed reduced DNA damage in leukocytes in patients undergoing platinum-based chemotherapy for urothelial, ovarian, or breast cancer while fasting for at least 48 hours when compared to patients who fasted for 24 hours or less. This study also observed no significant reduction in chemotherapy efficacy, suggesting fasting may be an effective adjuvant therapy to chemotherapy (Dorff et al., 2016). Bauerfeld et al. (2018) observed that short term fasting led to a better tolerance to chemotherapy, reduced fatigue, and a less compromised quality of life within 8 days after chemotherapy.

These studies, however, reported several challenges faced by patients undergoing fasting or a FMD during chemotherapy. There were complaints of dizziness, hunger, headaches, pyrosis, recurrent febrile neutropenia, and other grade 1 and grade 2 toxicities that resulted from fasting,

[1]It is important to note that some of these toxicities are sometimes also observed in patients with metastatic colorectal cancer who are not undergoing dietary MET restriction.

with patients even withdrawing from the studies due to side effects of the diet (de Groot et al., 2015; Safdie et al., 2009). Similar to the other metabolic approaches, patients who fasted reported significant weight loss and issues with compliance, sustainability, and palatability (de Groot et al., 2015; Safdie et al., 2009).

Furthermore, studies investigating the benefits of fasting during chemotherapy in human clinical trials involve smaller sample sizes and are limited. A lack of a large scale randomized human clinical study makes it difficult to draw significant conclusions on the efficacy of fasting as an adjuvant to chemotherapy.

Combined interventions

There are also case reports of combined interventions—interventions that involve multiple dietary approaches and therapies in addition to standard cancer therapy. Branca et al. (2015) presented a case report of a 66-year-old woman diagnosed with infiltrating adenocarcinoma of the breast. The patient's preoperative biopsy showed significant positivity, amplification, and overexpression (>10%) for the oncoprotein HER2—an important biomarker of breast cancer that is strongly associated with disease recurrence and poor prognosis — as well as low levels of progesterone receptor (PgR) expression (<1%), indicating a high level of tumor aggressiveness (Branca et al., 2015).

During the 3-week period between the diagnostic biopsy and the planned mastectomy, with no other planned treatment, the patient self-administered a strict KD supplemented with high doses of oral vitamin D3 and foods associated with high levels of glycosylated vitamin D-binding proteins (Branca et al., 2015). After 3-weeks of the combined intervention and mastectomy, an analysis of the specimen revealed no invasion of blood or lymph vessels around the tumor, and the patient's levels of HER2 and PgR expression went from >10% and <1% preoperatively, to negativity and 20% post-treatment, respectively (Branca et al., 2015). These results suggest that a combination of a KD with high-doses of vitamin D3 and glycosylated vitamin D-binding proteins may lead to significant changes in some of the biological markers of breast cancer.

İyikesici et al. (2017) reported a case of a 29-year old woman with stage IV invasive ductal carcinoma of the breast who underwent a metabolically supported chemotherapy in combination with a KD and hyperthermia and hyperbaric oxygen therapy. Prior to treatment, PET-CT scans revealed a primary tumor in the breast with widespread liver and lymph node masses, and an abdominal lesion (İyikesici et al., 2017). After 6 months of combination therapy, a mastectomy revealed that there was a complete clinical, radiological, and pathological response with no further evidence of disease found in the patient (İyikesici et al., 2017). Similar to a KD, hyperthermia and hyperbaric oxygen therapy exploit the defective energy metabolism of tumor cells and may contribute to DNA inhibition in cancer cells. The study found increased oxidative stress and oxygen radical production in tumor cells and tumor hypoxia—all factors leading to greater cancer cell death (İyikesici et al., 2017).

Both Branca et al. (2015) and İyikesici et al. (2017) reported cases where the advantages of a combined therapy can be seen— particularly in using multiple approaches to target the metabolic weaknesses of cancer cells in order to increase the overall anti-carcinogenic effects of treatment. However, both these case reports observed single patients. There is no large scale randomized controlled trial investigating the effects of combined interventions on cancer therapy in the context of human clinical studies, making it difficult to draw any conclusions (Fig.1). Further research is required.

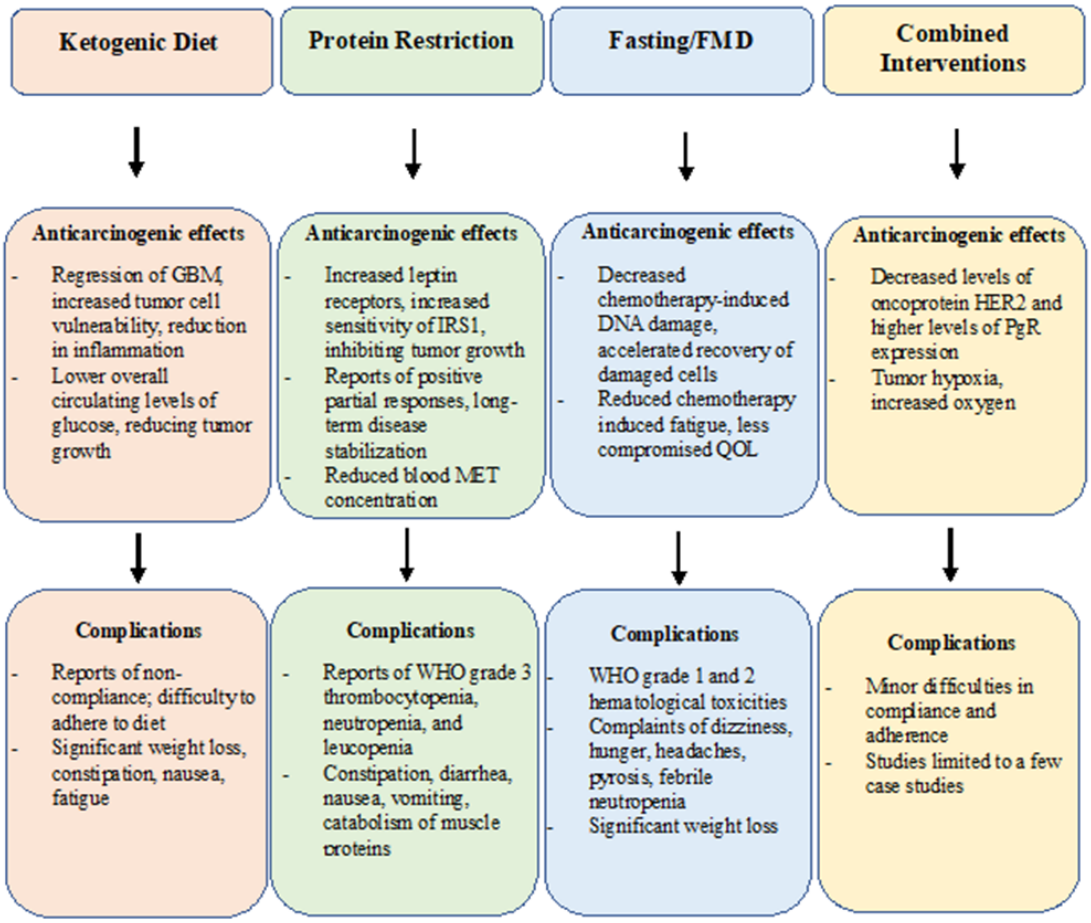

Figure 1. Schematic overview of the anticarcinogenic effects and complications of different diet-based approaches. Abbreviations: GBM; glioblastoma multiforme, IRS1; insulin receptor substrate 1, WHO; World Health Organization, QOL; quality of life.

Conclusion

Each of the four aforementioned diet-based therapies approach cancer in their own way. Although each of the therapies found instances of anticarcinogenic success in their clinical trials, complications and side effects were present in all studies. As previously stated, poor compliance, low palatability, weight loss, and poor sustainability were reported in each of the different diet approaches. The restrictiveness of KDs further presents a challenge of adherence, as most subjects were unable to follow the KD for the duration of their clinical treatments. As a result, the therapeutic use of KD may not be realistic until the diet's restrictiveness is addressed. Second, MET-free diets had greater levels of adherence from subjects, but low levels of protein consumption led to significant hematological toxicities such as WHO Grade 3 neutropenia and leucopenia. The therapeutic use of low protein diets should be limited to avoid harmful hematological toxicities. Next,

fasting and FMD subjects showed greater adherence than subjects on KDs, and lower toxicities than subjects on MET-free diets, but had a greater number of complaints of headaches, hunger, and dizziness than the other groups. Strategies to minimize these side effects or even help to deal with them may make fasting and FMDs an effective approach. Lastly, combined interventions have the fewest reports of side-effects and non-compliance. However, clinical trials of combined interventions are limited to a few studies and are relatively new. Nevertheless, the flexibility and range of combined interventions makes it the frontrunner as the most promising diet-based cancer therapy.

Although there are instances of significant benefits observed when metabolic interventions are combined with traditional cancer therapy, the lack of consistent, large-scale, and randomized trials in each of the four aforementioned approaches makes it difficult to form evidence-based conclusions on the anticarcinogenic effects of diet-based therapies. However, there are several clinical trials currently ongoing, which will lend valuable perspective and help to establish the effectiveness of diet-based therapies on cancers in the future. And although studies such as Zuccoli et al. (2010), Durando et al (2008), and Thivat et al (2009) are relatively dated, they provide insight into the potential feasibility and efficacy of different diet-based therapies, and present valuable information on the direction that future research needs to take, namely, prioritizing issues of adherence, compliance, and adverse side effects. As a result, these studies need to be further discussed, in addition to current clinical human trials, in order to identify key areas for future research. Researchers should continue to focus on randomized controlled clinical trials while developing strategies to minimize occurrences of non-compliance and adverse side effects.

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