



The Complementary Role of Exercise and Fasting in the Treatment of Cancer: A Narrative Review of Mechanisms Related to Metabolic Stress Elements

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Abstract

Background: Complementary methods such as physical activity (PA) and fasting are particularly important for cancer patients. The present study reviewed the effects of regular PA and fasting on cancer patients and attempted to explain the relevant mechanisms.

Methods: Several electronic databases such as PubMed, Elsevier, and Google Scholar were searched for keywords. After reviewing, 412 articles were identified until February 1, 2021. The inclusion criteria included meta-analysis, clinical intervention studies that considered different effects of fasting and various types of exercise on health indicators. After carefully reviewing and eliminating duplicates, 68 articles were identified based on the PICO format (participants, intervention, comparison, and results).

Results: The short-term fasting (STF) before chemotherapy (48-72 hours) or rehabilitation exercise could be modulating fasting blood sugar, growth factors, oxidative stress (OS), and inflammatory pathways. In addition, physiological metabolic stress induced by STF or rehabilitation exercise could regulate sex hormone-binding globulin, fat oxidation, leptin secretion, hyperinsulinemia, maintaining mass muscle, and bone density, boosting the immune system, and improving the therapeutic index of cancer.

Conclusion: Metabolic stress in cancer cells leads to the intake of high doses of chemotherapy. The rehabilitation exercise prevents the complications of the disease and improves the patient's quality of life. Thus, these interventions can be used to improve the cancer-based therapeutic index on individual differences.

Keywords: Fasting, Exercise rehabilitation, Metabolic stress, Cancer treatment

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Introduction

Cancer is one of the causes of mortality worldwide, and the number of people with cancer is increasing every year (1). On the other hand, the number of cancer survivors is increasing with advances in diagnosis and treatment. However, cancer and its treatment have various physical, mental, psychological, economic, and social consequences, including increased risk of heart disease/cardiotoxicity, decreased overall quality of life (QoL), cancer-related fatigue (CRF), and the formation of an inflammatory condition for the affected or improved person (2). In addition to the valid interventions/treatments, complementary methods such as physical activity (PA) and fasting are especially important for

these patients.

Research in the field of the exercise physiology of cancer patients began approximately 4 decades ago. By observing its beneficial effects on various aspects of patients' QoL, exercise as a rehabilitation intervention in this population was proposed in the mid-1990s (3). Regular exercise regulates fasting blood sugar, modulates growth factors, angiogenesis, oxidative stress (OS), and inflammatory pathways, and increases sex hormone-binding globulin (SHBG) and fat oxidation. Further, it reduces adipose tissue, fat percentage, leptin secretion, and hyperinsulinemia, maintains mass muscle and bone density and boosts the immune system, and consequently, improves the therapeutic index of cancer

(4-7). Adaptation to regular PA improves metabolic stress, immune function (8), cardiovascular function (9-12), antioxidant defenses, and inflammatory cytokines (13-18).

In addition to regular PA, fasting is also associated with a set of marked metabolic changes such as increased levels of free fatty acids, ketones, and activation of gluconeogenesis. Furthermore, fasting lowers insulin and insulin-like growth factor 1 (IGF-1) concentration and raises glucagon levels. This set of changes is called irregular metabolic exchanging or glucose-ketone alteration (19). Accordingly to some studies, the use of short-term fasting (STF) before chemotherapy programs was effective in increasing the use of toxins by cancer cells and simultaneously reducing the consumption of toxins by normal cells (20-22). It was also reported that this phenomenon is probably due to the modulation of cellular autophagy (23, 24).

Given the importance of regular PA and fasting as complementary interventions in the treatment of cancer, the present study focused on reviewing the effects of these two interventions on cancer patients and sought to explain the relevant mechanisms.

Methods

Some electronic databases (PubMed, Elsevier, and Google Scholar) were searched for keywords such as “Fasting”, “exercise rehabilitation”, “metabolic stress”, and “cancer treatment”. Overall, 412 articles were identified until February 1, 2021. The inclusion criteria were review and original articles investigating the effects of fasting and various types of exercise on health indicators. After careful review and elimination of duplicates, 69 articles were identified based on the PICO format (participants, intervention, comparison, results).

Regulation of Metabolic Stress Elements (Mechanisms Against Cancer)

Metabolic stress can occur pathologically or physiologically due to nutrient deficiency or overeating and the amount of available oxygen and can mostly affect the immune system (25). Accordingly, cells must be able to continuously restore energy homeostasis. The importance of studying this issue is that the immune system plays a vital role against cancer, and the research literature indicates the existence of complex, multifaceted relationships between metabolic status, inflammatory responses, and the immune system (26).

The two main signaling pathways, mTOR and eIF2 α , play a significant role in modulating immune responses under metabolic stress conditions. The most important regulators of these pathways are the adenosine triphosphate/adenosine monophosphate (ATP/AMP) ratio, increased glucocorticoid levels, and amino acid availability, as well as the binding of free fatty acids to

TLR4 and OS (25, 27-29). The immune system is directly and indirectly activated by modulating the ability to respond to pathogens. Direct activation involves the immune cell response called the ‘acute phase molecular’. On the other hand, in indirect conditions, metabolic stress activates immunity by inducing a heat shock response (HSP) or producing stress proteins. Known acute-phase molecules include HMGB1 protein, S100 protein, uric acid, and HSP70 heat shock protein, which are essential in cancer treatment (30). In general, the consequence of activating the immune system by metabolic stress is the development of an anti-inflammatory process involving the production of cytokines against antigens.

Metabolic stress can be related to many factors such as insulin resistance, obesity, fatty liver, type 2 diabetes, and OS. The relationship between OS caused by obesity and its effect on developing metabolic disorders, including insulin resistance, is an exciting issue (31). Obesity in humans exacerbates metabolic stress with higher expression of proinflammatory cytokines, increased lipolysis, interference with liver function, decreased insulin sensitivity, and increased OS (6). Note that obesity and high-fat percentage are highly associated with cancer (4).

Previous evidence shows that high-fat diets and certain foods cause inflammation in the white adipose tissue. Hypertrophic fat cells significantly increase inflammation and intracellular OS by altering leptin production. OS alters the function of many vascular endothelial cells, myocytes, and pancreatic β cells and can lead to cancer (32). OS is an influential factor in metabolic changes associated with obesity and cancer. Metabolic stress and PA can counteract these two factors by reducing adipose tissues and antioxidant adaptations.

Studies on the interaction of signaling pathways demonstrate that the relationship between nutrition and metabolic stress plays a vital role in the progression and treatment of diseases (33). Accordingly, insufficient or excessive consumption of several nutrients can significantly disrupt cellular homeostasis, activate molecular pathways, and change the metabolic status of various tissues by nearly 30%-35% (34). High levels of nutrient metabolism lead to the production of OS, leading to the progression of diseases such as cancer through the activation of oncogenes (26). Obesity seems to play various roles in different types of cancer through a combination of hyperinsulinemia, low-grade systemic inflammation, alteration of cell surface proteins, and their glycosylation (4, 5, 7, 35, 36).

In contrast, it has been accepted that controlled dietary restriction (DR) can lead to cellular adaptation and reduce age-related diseases, especially dementia (37). Two different models are typically used for DR modeling in research projects. In one approach, the animals receive food daily, but the amount of food is reduced by approximately 40%-30% of the subject’s preferred intake

(ad libitum: AL) according to the experimental design. In the second model, called 'intermittent fasting' (IF), food is prepared for the subject during specific periods, while at other times, he does not have access to food (change of meals). For example, the subject is deprived of food for a full day, one day between, once every three days, and fed AL on other days. In another version, subjects follow an IF program but receive smaller amounts of AL food on feeding days (37, 38). Despite the differences in these methods, body mass parameters, temperature, heart rate, blood pressure, glucose, and insulin levels are commonly used for measuring metabolic stress. Various molecular mechanisms are believed to be responsible for the beneficial effects of DR, including improved insulin signaling, altered function, mitochondrial biogenesis, and decreased stable levels of reactive oxygen species (39).

For metabolic responses to IF, animal and human subjects should be exposed to this diet for at least four weeks. At the end of this period, the intervention groups have nearly 5%-21% less body mass compared to the control groups. Plasma glucose and lactate levels also decreased significantly after one day of fasting, while the activity of alanine aminotransferase and aspartate aminotransferase represented an increase. These results, along with lower cholesterol levels, indicate that fasting people rely on lipid oxidation (19, 40). On the other hand, the serum cortisol concentration (as a factor affecting the immune system) of fasting people increases 1.8 times after 24 hours. Fasting also modulates the daily secretion pattern of cortisol by delaying the maximum serum concentration until the early afternoon (41).

However, hemoglobin levels in both men and women do not appear to be affected by IF. Instead, the number of male red blood cells under IF increases significantly (hemoconcentration). Moreover, IF can drastically reduce the number of leukocytes in men and women. These effects may indicate a reduction in the inflammatory process and replace damaged immune cells with new ones (29). The results demonstrate an increase in the number of divided neutrophils, while a decrease in fasting lymphocytes, especially in women. A relative increase in the neutrophil count can also occur under stress and after strenuous PA. These changes can be due to the positive response of the immune system to the stress of fasting (19, 42).

In addition to signal pathways associated with diets, metabolic stress is also caused by muscle contractions (27). During PA, the energy used in muscle contraction plays a vital role in cell organs, enzymatic activity, intracellular signaling, and cell gene expression. Accordingly, metabolic stress is a physiological process that occurs during exercise in response to an energy crisis and leads to the accumulation of metabolites such as lactate, inorganic phosphate (Pi), and hydrogen ions (H⁺) in muscle cells. The formation of these metabolites through endocrinological changes, hypoxia, and OS significantly

affect muscle hypertrophy (25, 27-29). In this process, increased anaerobic metabolism leads to a significant reduction in skeletal muscle adenine nucleotides and the release of ammonia during the irreversible process of converting AMP to inosine monophosphate, resulting in fatigue in healthy individuals and some patients when doing high-intensity exercise (9, 16, 18, 43). Thus, plasma ammonia accumulation results from adenine nucleotide loss and metabolic stress and is potentially considered a biomarker of the muscular energy response. Depending on the type of exercise, a concomitant increase in ATP hydrolysis and glycolytic flux, high AMP accumulation, and decreased intracellular oxygen levels can lead to hypoxia. These metabolic parameters are a potent stimulus for activating the protein kinase pathway and the HIF-1 α induction pathway as significant regulators of mitochondrial biogenesis and capillary depletion (9, 16, 18, 25, 27-29, 43). On the other hand, moderate use of these exercises in rehabilitation courses is recommended due to the maintenance of muscle mass. This effect of PA is similar to a double-edged sword, and each person and patient must use a unique method.

In resistance training, metabolic stress and stimulating biogenesis and mitochondrial angiogenesis have positive effects on the muscular system. Hypertrophic responses to resistance training result from various hormonal, metabolic, and mechanical factors (16, 17, 27, 44). Part of this response is the activation of hypertrophy signaling pathways in the muscle, including activating the calcium-calmodulin pathway (PI₃K/AKT) and MAPK (the main pathway for gene expression, regeneration, and metabolism in the mitochondria). All these signaling pathways are activated during resistance training due to the development of metabolic stress in the muscle (9, 16, 18, 25, 27-29, 43). Metabolic stress also increases the production of anabolic myokines such as interleukin-15 by releasing IGF-1 and decreasing muscle catabolic factors. In this regard, some techniques can be used to increase muscle lactate and blood urea levels and exercise with limited blood flow (Katsu) to increase muscle metabolic stress (45).

Oxygen is usually used throughout the body to reduce ATP circulation in continuous aerobic exercise (AE), and muscle strength is applied in short-term exercise. Other specific quantification methods include measuring the substrate, muscle enzymatic activity, heat generation or accumulation of metabolites (lactate, hydrogen ions, ammonia, and hexose monophosphate), and molecular techniques (46). The degree to which each of the nervous, cardiovascular, endocrine, and respiratory systems is activated can also indicate a response to metabolic stress. However, each of these systems is unique in terms of its threshold and sensitivity to metabolic stress. Cardiac output, systolic blood pressure, heart rate, muscle blood flow, and plasma norepinephrine concentrations increase

linearly by an increase in AE and ventilation, muscle glycogenosis, and plasma epinephrine concentrations increase non-linearly by increasing metabolic stress (47).

Metabolic stress depends on the exercise mode, intensity, exercise duration, fitness, nutritional status, and environmental factors (16, 48). Concerning the type of exercise, long, low-intensity walking causes little metabolic, hormonal, or cardiovascular stress. Similarly, most of the confusion in fasting is due to increased fat oxidation and plasma fatty acid mobilization (49). Slow to vigorous running greatly stimulates the oxidation of intramuscular glycogen and triacylglycerol, increasing oxidative capacity and mitochondrial function. On the other hand, 15 resistance contractions cause high utilization of the motor unit and stimulation of muscle fibers and are a powerful stimulus for changing muscle protein synthesis and increasing neuromuscular function (46, 47, 49). In these exercises, the amount of metabolic stress can be changed by manipulating the number of repetitions and the rest time. According to different studies (9, 16, 18, 25, 27-29, 43), high-repetition training protocols (increased blood lactate response, growth hormone, insulin, and cortisol) led to more metabolic stress compared to high-intensity training protocols (increased myoglobin and blood lactate dehydrogenase). In contrast, short rest intervals (30 seconds) resulted in tremendous metabolic stress compared to longer rest intervals (90 seconds) and were associated with higher levels of blood lactate, growth hormone, epinephrine, and norepinephrine (28). Other factors affecting the amount of metabolic stress in PA are genetic status, age, and gender (45, 49). Briefly, it is better to use light intensity training exercises based on VO_{2Peak} in clinical conditions (Figure 1).

Discussion

In summary, controlled metabolic stress elements from dietary manipulation or regular PA through cellular

and molecular mechanisms can advance the healing process in patients undergoing chemotherapy. Essential physiological mechanisms of this important event will be discussed in the following section.

One of the main challenges in the fight against cancer is to limit the effects of treatment methods and find strategies to reduce the toxic effects of chemotherapy or the side effects of radiotherapy and bone marrow transplantation (3, 8). The positive effects of religious fasting on diabetes control have been studied and confirmed as one of the causes of cancer (50). Chronic caloric restriction has been suggested to positively affect the improvement of cancer in humans (22). A significant reduction in the incidence of lymphoma and a reduction in the development of spontaneous tumors in mice with p53 deficiency (as a tumor suppressor) was also reported by another study (39). The results of chronic calorie restriction in humans indicate a reduction in metabolic and hormonal factors associated with cancer due to stem cell renewal, strengthening the oxidation system and the killer cells of the immune system. However, chronic caloric restriction in cancer patients due to apparent problems such as the required length of time and reduced net body mass requires careful individual examinations (20, 39). On the other hand, IF alters the biological cycle of the body by changing the patterns of nutrition, sleep, and daily habits and acts as a stressful stimulus for the patient's physiological environment (37).

Clinical studies demonstrate that STF protects rodents from the toxic effects of chemotherapy and simultaneously enhances the effects of chemotherapy agents on many distinct malignancies. Accordingly, the tumor size, metastasis rate, and tumor metabolism rate in response to chemotherapy combination with STF 24-60 hours represent a significant reduction (20, 51). This issue has also been studied and confirmed in human studies (22). Fasting based on the direct relationship between the effects of chemotherapy and metabolic activity also

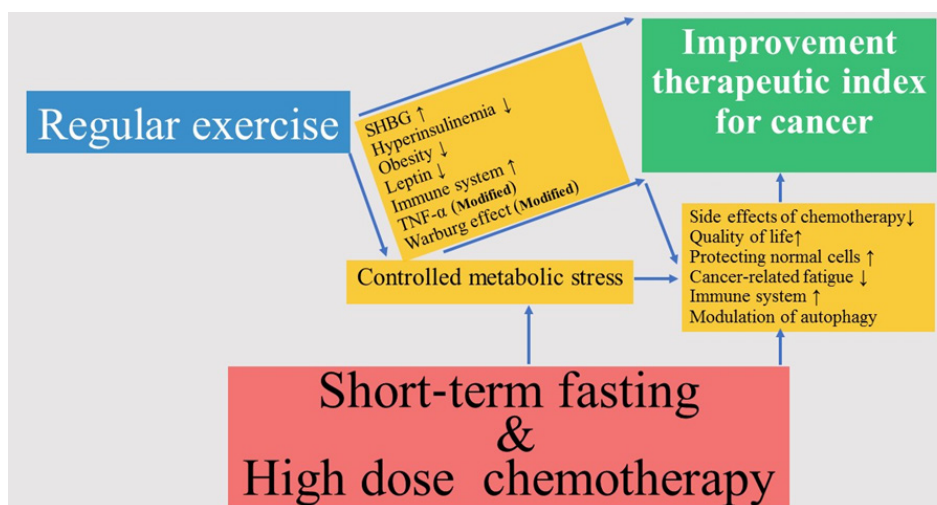


Figure 1. The Effect of Physiological Metabolic Stress Induced by Fasting or Exercise Rehabilitation on Improving Cancer Treatment Indices.

induces protective mechanisms against the side effects of chemotherapy (20, 42).

Another essential factor in STF is the modulation of cellular autophagy (23, 24). During nutrient deprivation, healthy cells make the most of intracellular stores, survival mechanisms, and organ protection by minimizing cell growth and proliferation pathways. Contrarily, cancer cells continue to maintain high metabolic activity (52), which leads to the overuse of chemotherapy toxins by cancer cells (22-24). The effect of STF refers to differential stress resistance, which protects healthy cells from stress (20, 53). In this process, healthy cells store their energy to maintain and repair cells, while cancer cells cannot slow growth. Moreover, low serum glucose levels and a concomitant increase in tumor necrosis factor alpha (TNF- α) during STF impose more strains on tumor cells because their energy needs are primarily met by glycolysis (54). As a result of these differential responses, chemotherapy causes DNA damage and apoptosis in cancer cells, while healthy cells demonstrate no damage. Thus, STF, based on a phenomenon called differential stress sensitization (along with differential stress resistance), protects healthy cells from the toxic properties of chemotherapy and sensitizes tumor cells (20, 55). STF further increases the QoL and reduces fatigue after chemotherapy (22, 56).

In a study of the optimal duration of fasting in combination with chemotherapy, the researchers found that 72 hours of STF normalizes the number of lymphocytes and maintains an average balance of white blood cell counts (lymphoid/myeloid ratio) in the course of chemotherapy. However, fasting for 24 hours does not indicate such results. IGF-1 levels also decreased by nearly 30, 33, and 8% in the 24, 48, and 72-hour fasting groups, respectively. The rate of DNA damage in the leukocytes of people fasting for more than 48 hours decreased compared to those in the group of 24-hour fasting (57), and this was due to the activation of the signals of adaptation to controlled fasting. It should be noted that fasting means shifting meals or reducing the number of meals instead of reducing the total calorie intake.

Overall, STF is a new strategy for increasing the effectiveness of chemotherapy in a wide range of cancers. Many patients have reported that they tend to continue fasting due to reduced complications of chemotherapy (58). However, malnourished patients and people on corticosteroid regimens may not be suitable options for STF interventions. Recent guidelines recommend increasing protein and fat intake in some cancer patients to avoid interfering with the benefits of STF (35). Clinical research on the potential effects of fasting on cancer is still in its infancy, and more research is needed on the exact mechanism and effects of this intervention.

Additionally, exercise interventions are known to be completely safe and beneficial for patients undergoing treatment, contributing to their health and function (8).

However, a range of considerations of health status, clinical history, functional abilities of the person under treatment, and access to sports specialists further challenge sports recommendations. On the other hand, most studies have examined different exercise protocols in a particular type of cancer or a cancer-related disorder. Nonetheless, there are many questions about the type of exercise, the optimal time, repetitions, duration, and intensity of exercise. Accordingly, prescribing sports interventions in cancer care programs requires more accurate guidelines for identifying standard features (59).

In addition to the fact that exercise is one of the strategies for cancer prevention, evidence suggests that these activities effectively control cancer progression by mobilizing and activating cytotoxic immune cells, limiting the inflammatory signaling pathways of myeloid cells, and regulating other inflammatory responses (60). Therefore, exercising in the early stages of cancer treatment is probably the most beneficial time to reduce the side effects of chemotherapy and make significant progress in this regard. This function makes it possible to discover different conditions such as resistance-based exercise, exercise intensity, the potential effect on hypoxia of the tumor, and the applied chemotherapy drugs (2, 3, 8).

Regular exercise positively affects several aspects of the QoL of cancer patients (61). In this regard, AE and physical-mental exercise (MBE) improve patients' quality of sleep. Contrary to the effects of mental exercise, the effects of AE remain significant after 3 to 6 months (62). On the other hand, CRF is the most common and distressing symptom in 40-80% of cancer patients. In this regard, exercise interventions, including 6 weeks of aerobic, resistance, and stretching exercises (40 minutes per session) improve CRF symptoms at any stage of cancer (63). There is also evidence regarding the effectiveness of resistance training in maintaining bone mineral density and lean body mass, and improving physical performance outcomes in men with prostate cancer (64) and women at risk for breast cancer (65). These findings suggest that these exercise protocols should be considered an essential part of the rehabilitation program for cancer patients.

Although cancer patients are advised to follow general PA guidelines, according to the first American College of Sports Medicine exercise guidelines, regular PA, in addition to significant health benefits, reduces the risk of some cancers by strengthening the immune system. The minimum amount of PA required to achieve such an advantage is still unknown, but the equivalent of at least 150 minutes of moderate-intensity PA is necessary (66). On the other hand, according to the latest research findings, regular, intense exercise (6 METs or more) prevents changes in the progression and recurrence of colorectal, breast, and lung cancers by altering the immune system, metabolism, hormones, systemic inflammation, angiogenesis, and cellular redox balance.

The patients undergoing these interventions are more confident about their health status and show less fear of cancer recurrence compared to sedentary patients (67). An essential point in these exercises is the tendency of patients to use antioxidant supplements when participating in exercise programs. Considering that the production of TNF- α , HSPs, and controlled OS from PA is one of the causes of tumor destruction, antioxidants during exercise neutralize the beneficial effects of exercise on tumor growth in human and animal models. On the other hand, antioxidants may interfere with radiation therapy or chemotherapy (66, 67).

For patients suffering from weight loss, muscle wasting, fatigue, anemia, and cardiorespiratory problems, moderate to extreme endurance or resistance training is limited. The complex interaction of metabolic disorders and muscle homeostasis challenged the development of reliable therapeutic interventions. Although exercise in these conditions is not typically the first line of clinical treatment, its ability to reduce systemic inflammation and promote anabolic processes is significant. New evidence suggests the potential of exercise to increase muscle sensitivity to anabolic stimuli, reduce muscle wasting, release myokine, regulate proteolytic agents, and improve muscle mitochondrial function. Resistance training helps maintain muscle tissues and convert the white adipose tissue to brown adipose tissue by PGC1 α -FNDC5-BDNF axis signaling pathways (16, 44, 68).

Overall, the natural cells of the body have the properties to sustain life under metabolic stress conditions. For example, due to lactic acid production, the glycolysis of normal cells is limited and short-lived under these conditions. Contrarily, cancer cells, due to the high expression of the MCT-4 gene, have a high ability to consume sugar and rapid excretion of lactate and thus continue their metabolic process and life through glycolysis, and this is called the 'Warburg effect' (4, 54). Accordingly, sugar consumption and hyperinsulinemia conditions significantly affect the growth and development of cancer cells. However, hyperinsulinemia, obesity, and increased leptin secretion from various signaling pathways, including inhibition of SHBG production, promote the growth and development of cancer cells (4, 6). Note that fasting and regular exercise reduce antigen transcription and tumor growth by controlling blood sugar, reducing adipose tissue, and subsequently reducing leptin secretion (19).

On the other hand, one of the reasons for using chemotherapy is the consumption of more toxic substances by cancer cells compared to normal cells. The effect of chemotherapy will increase if STF is used before this treatment (20, 51). The cause of this physiological phenomenon is the adaptation of natural cells to conditions of metabolic crisis. Natural cells use internal reserves in these conditions. Conversely, this feature is

unavailable in cancer cells, increases the consumption of food under metabolic stress conditions, and increases the likelihood of its destruction due to the overuse of chemotherapy drugs (21, 53). These benefits of metabolic stress can be caused by fasting or regular PA. However, the simultaneous use of these two factors (especially in patients and certain groups) is not recommended at all.

Conclusion

Pathological metabolic stress caused by total caloric intake increases the likelihood of cancer cells producing large amounts of energy. In contrast, regular physical exercise, in addition to the positive physiological and psychological effects, reduces the metabolism of cancer cells by reducing ATP/ADP, modulating the expression of GLUT-4 and TNF- α , and destroying tumors (8, 66). TNF- α , which increases in response to acute PA, prevents glucose from entering cells, especially tumors. However, excessive secretion of this cytokine in response to intense activity is a cause of fatigue. Therefore, it is precious to consider an optimal intensity rate based on the patient's peak oxygen consumption (VO_{2Peak}) and to observe the principle of gradual overload. However, the antioxidant defenses and inflammatory pathways of TNF- α and Nf κ B are modulated in response to regular PA (adaptation) (13-17).

In this regard, understanding the cellular mechanisms of the effects of exercise on cancer can identify new ways to improve the care of cancer patients. The severity and optimal duration of PA in future studies should be more carefully defined to identify the most effective behavioral interventions for achieving long-term lifestyle changes in patients. Due to the complexity of providing cancer services during coronavirus disease 2019 (COVID-19), many people under treatment cannot access sports services. Therefore, new methods (e.g., exercise at home and telecommunication technology) are helpful approaches for improving patients' physiological and psychological capacities during hospital discharge (11). It also prepares the metabolic stress of fasting cancer cells for high-dose chemotherapy. Natural cells, on the other hand, receive fewer toxins by relying on internal reserves. Regular exercise (6 METs or more) prevents the secondary complications of the disease and improves the patient's QoL and function by affecting biological systems. It is noteworthy that this is the intensity of the target, and the patient should gradually approach this range. Therefore, based on individual differences, these interventions can create metabolic stress and strengthen the immune system in the prevention and treatment of cancer. Finally, it should be noted that regular PA and diet control are not just complementary therapies in the healing process of cancer; they prevent many secondary cardiovascular complications due to inactivity during treatment. Exercise training improves the function of the cardiovascular system (12) through reverse cholesterol

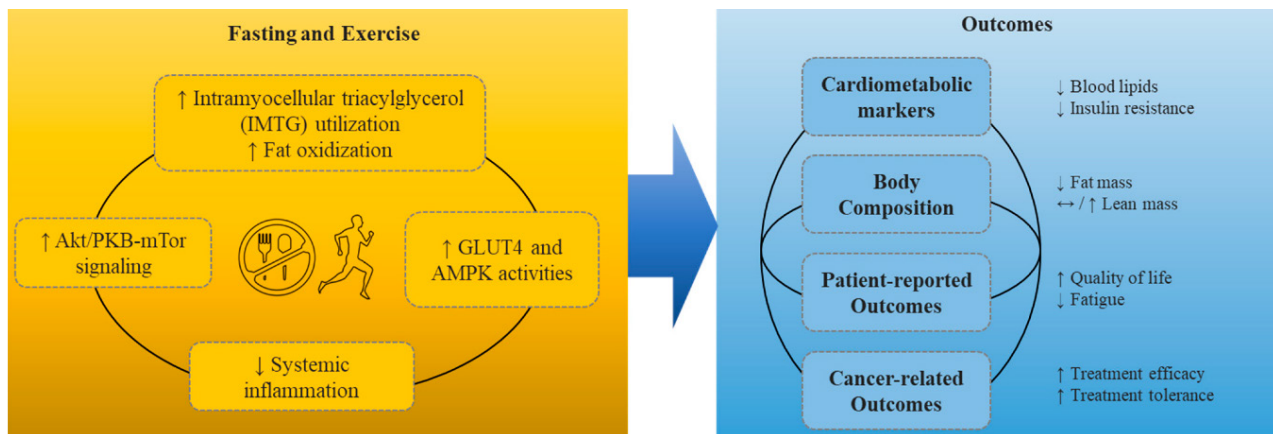


Figure 2. Some of the Mechanisms Related to the Effects of Fasting and Exercise on Cancer Patients (69).

transfer (9, 10). However, it is imperative to pay attention to the stages before, during, and after treatment and treatment methods such as chemotherapy or bone marrow transplantation.

If STF in cancer patients has shown promising results, it is necessary to study different periods of fasting in healthy people to prevent diseases. It is also necessary to review a wide range of studies on the effects of different sports exercises. The study of metabolic stress as a common aspect of fasting and regular PA should also be considered in study projects. Finally, it is worth noting that a definitive opinion is still somewhat out of reach, but promising results confirm the impact of lifestyle modifications through diet control and regular PA on the prevention and treatment of diseases, especially cancer (Figure 2).

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Authors' Contribution

H. F. and S. R. A. participated in investigation, methodology, project administration, resources, and software. M. H., M. Z., H. F., S. R. A., H. M., S. F., H. D., and J. Y. did investigation, methodology, project administration, resources, software, formal analysis, conceptualization, supervision, data collection, original draft writing, review writing, and editing.

Disclosure Statement

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