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REVIEW ARTICLE

SIGNIFICANCE OF LOW-CARBOHYDRATE DIETS AND FASTING IN PATIENTS WITH CANCER

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ABSTRACT

The differences between the metabolism and the physiology of cancer cells and the cells of the human body are assessed and used in most anticancer treatments. These differences encompass, among others, increased glucose metabolism in the changed cells. The aim of the paper was to discuss the results of studies concerning the relationship between low-carbohydrate diets and fasting and the course of cancer. An inappropriately composed diet consisting of high amounts of simple sugars supplies cancer cells with nutrients, which may impair the effectiveness of cancer patients treatment. Low-carbohydrate diets may, therefore, constitute an element of supplementary therapy in cancer treatment. The mechanism of low-carbohydrate diets in combination with standard treatment has not been completely explained, though. In initial studies it was proven that patients who were able to continue low-carbohydrate diets showed improvement in health and reduction of tumor mass or its slower growth. Moreover, it was observed that the inability of cancer cells to adapt in new environmental conditions that occur while fasting may have toxic effect on them. Introduction of fasting may sensitize cancer cells to chemotherapy, decrease concentration of growth factors and lead to repair of normal cells. On the other hand, fasting may also promote autophagy and, as can be concluded from the literature, its mechanism may have twofold activity: as a process impacting the survival or death of cancer cells.

Key words: *cancer, fasting, intermittent fasting, low-carbohydrate diets, ketogenic diet*

STRESZCZENIE

W większości terapii przeciwnowotworowych oceniane i wykorzystywane są różnice między metabolizmem i fizjologią komórek nowotworowych, a komórkami ciała człowieka. Różnice te obejmują między innymi nasilony metabolizm glukozy w zmienionych komórkach. Celem pracy było omówienie wyników badań na temat związku diet niskowęglowodanowych i głodówek z przebiegiem choroby nowotworowej. Nieodpowiednio skomponowana dieta składająca się ze znacznej ilości cukrów prostych dostarcza składniki odżywcze komórkom nowotworowym, co może pogarszać skuteczność leczenia pacjentów onkologicznych. Diety niskowęglowodanowe mogą więc stanowić element terapii uzupełniającej w chorobie nowotworowej. Mechanizm działania diet niskowęglowodanowych w połączeniu ze standardowym leczeniem nie został jednak w pełni wyjaśniony. We wstępnych badaniach wykazano, że pacjenci, którzy byli w stanie kontynuować diety niskowęglowodanowe wykazywali poprawę stanu zdrowia, zmniejszenie masy guza lub jego spowolniony wzrost. Ponadto zaobserwowano, że niezdolność komórek nowotworowych do adaptacji w nowych warunkach środowiska, jakie występują podczas głodzenia, może działać na nie toksycznie. Wprowadzenie postu może uwrażliwić komórki nowotworowe na chemioterapię, zmniejszać stężenie czynników wzrostu i prowadzić do naprawy prawidłowych komórek. Z drugiej strony post może również promować proces autofagii, a jak wynika z piśmiennictwa, jej mechanizm może mieć działanie dwukierunkowe: jako proces wpływający na przeżycie lub śmierć komórek nowotworowych.

Słowa kluczowe: *choroba nowotworowa, głodówka, post przerywany, diety niskowęglowodanowe, dieta ketogenna*

INTRODUCTION

In epidemiological studies it was proven that diet plays key role in the process of carcinogenesis. Obesity and metabolic imbalance related to sedentary lifestyle and consumption of wrong foods may induce oxidative stress, insulin resistance and hormonal changes that are significant in cancer pathogenesis. Inadequate diet is understood as excessive consumption of meat and processed foods and insufficient consumption of plant foods, among others vegetables, fruit, legumes and whole-grain products [37, 59, 66].

Metabolic processes in cancer cells are different than in healthy cells. One of the most frequent

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metabolic changes in cancer cells is increase in glycolysis speed even in the presence of oxygen. The authors confirm the hypothesis according to which metabolism of cancer cells depends on higher supply of glucose for maintenance of *redox* homeostasis related to increased reduction of O_2 to O_2 •−and H_2O_2 electrons in mitochondria. In cancer cells, process of glucose fermentation into lactate occurs even with adequate availability of oxygen. The effect, known as the *Warburg* effect, constitutes a separate characteristic feature of cancer cells and may be caused by genetic mutation. Authors of research [1, 60, 77] works made an attempt to reduce the amount of carbohydrates in diet, in order to selectively sever the energy supply to cancer cells and, thus, inhibit tumor growth.

The aim of the study was to assess the relationship between low-carb diets and fasting, and the course of cancer on the basis of literature review.

CANCER CELL METABOLISM

In most anti-cancer therapies the differences between the metabolism and the physiology of cancer cells, and human body cells are assessed. Cancer cells are characterized by different metabolism in comparison to properly differentiated cells. These differences encompass, among others, increased glucose metabolism that depends on many factors, including increased activity of the GLUT glucose-transporting proteins and some enzymes as well as the level of proliferation. Cancer cells show high level of proliferation; the consequence of it is disturbance in access to nutrients, including glucose and oxygen, and, as a result, switching cell metabolism to anaerobic respiration. Glycolysis becomes the main process in which energy, in the form of high-energy bonds of adenosine triphosphate, is produced (ATP). Pyruvate, produced in the glycolysis process, is transformed by lactic fermentation into lactic acid [6, 40]. The above phenomenon was more broadly described in the second half of the 20th century by a German scientist, *Otto Warburg*. In the research conducted in animal models within the last 60 years, increased uptake of glucose by cancer cells in comparison to the normal cells has been confirmed. Using positron-emission tomography (PET), the authors of the study observed an increased uptake of glucose and release of lactate by malignant cancer cells in comparison to benign cancer cells [68]. It seems that depriving cancer cells of energy source, namely glucose, may result in inhibition of their proliferation which may be related to higher effectiveness of radio- and chemotherapy [40].

Hyperglycemia is of high significance for growth and proliferation of cancer cells. An inadequately composed diet, consisting of high amounts of simple carbohydrates, provides cancer cells with nutrients, which may negatively affect the effectiveness of cancer patients treatment [15, 19]. Thus, a thesis stating that low-carbohydrate diets may constitute an element of supplementary therapy in cancer has been formulated. Energy production from fats decreases availability of glucose to glycolysis and decreases production of pyruvate and glucose-6-phosphate which may enter the pentose phosphate pathway creating nicotinamide adenine dinucleotide (NADPH) necessary for hydrogen peroxide reduction. As a consequence, lack of NADPH regeneration increases the dynamic of oxidative stress in cancer cells. Lipid metabolism in cancer cells is, in addition, related to the use of energy from mitochondrial metabolism. In cancer cells, damaged respiratory chain in mitochondria occurs. It is related to increased reduction of O_2 electrons that leads to synthesis of reactive oxygen species (ROS) [10, 12]. Many amino acids enter the tricarboxylic acid cycle in the course of the *Krebs* cycle. This process may be related to gluconeogenesis, allowing for NADPH production. Protein metabolism cannot therefore lead to increase in ROS production in cancer cells on the same level as metabolism of fats [34]. Glutamine is used as a substrate and a donor of nitrogen atoms for cancer cells. It enters the *Krebs* cycle by transforming into glutamate and then into α-ketoglutarate. As a result of further transformation, α-ketoglutarate may undergo gluconeogenesis, allowing for production of NADPH [95]. *Lieberman* et al. [48] observed that cancer cell lines that they were analyzing showed higher uptake of glutamine than of glucose. Metabolic changes of glutamine may influence protection of cancer cells from oxidative stress and promote tumor growth [16,17]. In restrictive conditions, cancer cells also use ketone compounds as energy source. It is possible only in the presence of adequate oxygen concentration, access to which is limited during fast growth of tumor [30]. *Lin* et al. [49] observed presence of enzymes which condition oxidation of fatty acids in the cells of human glioma. Fatty acids were used as the main energy source by cancer cells.

THE MECHANISM OF FASTING AND AUTOPHAGY IN THE PROCESS OF CARCINOGENESIS

The term autophagy comes from Greek and means self-consumption. It is an intracellular process that consists in degradation of macromolecular components of cytoplasm [50, 61]. The process of autophagy may be induced by many factors, including fasting, oxygen deprivation, damage to DNA structure and hormone activity [50]. Autphagy ambiguously influences the stages of neoplasm initiation and progression. It is related to overlapping of signal pathways of autophagy and carcinogenesis. In chronic autophagy inhibition

carcinogenesis is promoted, which is related to genome instability, defective cell growth and oxidative stress induction. However, increase in autophagy process may be related to a mechanism that allows for survival of cancer cells in the state of oxygen deficiency, acidosis and under the influence of chemotherapy. Due to those factors the process of autophagy in cancer development should be considered in a two-way manner [56, 94].

The process of autophagy is used as a mechanism that conditions survival of cancer cells and may be inhibited at the early stages of cancer which allows for tumor development. At the late stage of cancer, autophagy and intercurrent cancer cell resistance to chemotherapy are increased [47, 56, 79]. For example, increased autophagy is used in liver cancer cells in order to provide key medium metabolites that are necessary for maintaining energetic processes at the level that allows for cell survival [97].

Autophagy may also act in a completely opposite manner, contributing to cancer cell elimination causing their apoptosis and increasing the effectiveness of treatment. Hunger is one of the most effective ways of promoting autophagy in cancer cells; it enhances immunological response and treatment process in cancer patients [79, 94]. In cancers with mutation in the *Ras* oncogene (including lung cancer, colon cancer and pancreas cancer) increased autophagy, necessary for cell growth, was observed. This process is necessary for cells both at the stage of transformation and at the stage of progression. *Lock* et al. [51] observed that autophagy blocking in cancer cells with *Ras* oncogene mutation was related to the decrease of their proliferation potential. In addition, inhibition of autophagy process decreased the ability of cancer cells to use glycolysis. *Van Niekerk* et al. [86] proved higher immunity of normal cells to negative effects of applied chemotherapy when fasting was introduced. Fasting was related to physiological adaptations, including regulation of autophagy. According to the authors, these processes could have influenced the effectiveness of chemotherapy.

Thus, the role of autophagy in the carcinogenesis process is not unambiguous, because it depends on the type of cells and the conditions in which they dwell. Further studies are needed in order to understand these processes better.

VERY LOW CALORIE DIETS

While fasting, energy expenditure is decreased and used in processes that are aimed at organism protection and that condition survival [52]. Proliferation of cancer cells occurs in an environment rich in nutrients, in which processes such as glycolysis and protein biosynthesis can take place. Inability of cancer cells to adapt in new environmental conditions that occur during fasting may have toxic effect on them [65]. The difference between tumor-induced weight loss (TIWL) and fasting is that in the case of cancer cachexia the process cannot be reversed after introducing proper nutrition. It is assumed that cancer cachexia means unintentional weight loss by 5-10% within 6 months. TIWL is observed in, among others, patients with advanced stomach cancer, pancreas cancer, lung cancer and colon cancer. Despite the development in the field of oncology, TIWL remains a significant cause for persisting chronic illness and morbidity of cancer patients [8].

In the research by *Sun* et al. [79] the relationship between the applied fasting and the organism's immunity to cancer was assessed. The authors of the research observed that introduction of fasting for the period of two weeks caused inhibition of tumor growth in mice, without causing decrease in their body weight. It is one of the first works in which the above dependency was described. It was proven that introduction of fasting may induce autophagy in colon cancer cells, which eventually inhibited tumor growth by promoting anti-cancer immunity. From pre-clinical studies, conducted in animal models, it can be concluded that calorie restriction (CR) positively influenced lifespan and delayed occurrence of illnesses related to aging of the organism, including cancers. The above method of nutrition is described as calorie restriction by about 20 - 40%, without allowing for the occurrence of the state of malnutrition [31]. Metabolic changes related to calorie restrictions positively influenced health, including increase in insulin sensitivity, decrease of inflammation and inhibition of angiogenesis [11, 32, 55]. In addition, introduction of CR influenced processes that are directly related to the pathomechanism of cancer, including repair processes of the DNA, removal of damaged cells in result of apoptosis, increased autophagy and protection from toxic factors [14].

Calorie restriction in diet and health benefits related to it are observed in various countries, for example in Japan. High diversification in terms of life length was observed there. The inhabitants of the Okinawa prefecture lived the longest, which is believed to be caused by their traditional, healthy lifestyle which can be characterized as CR [80]. *Suzuki* et al. [80] observed that the people from the island consumed 17% less calories in their diet in comparison with the people living in continental Japan, and 40% less calories than an average resident of the United States. The authors state that the residents' diet consisted mainly of fresh vegetables, fruit, sweet potatoes, soy and fish, and the share of energy from protein in the diet was 9%. Morbidity due to cancer, including prostate, colon and breast cancer, was much lower in comparison with Japanese and American populations [36].

INTERMITTENT CALORIE

Intermittent calorie restriction (ICR) consists in calorie restriction in a diet for 1-3 days per week. *Kusuoka* et al. [45] studied the influence of ICR in mice with induced colon cancer. The mice were subjected to a 24-hour-long fasting once a week for four weeks. The control group received high calorie diet or diet rich in *trans* fatty acids. It was observed in the study that ICR had no tumor growth suppression effect, and the applied nutrition model promoted proliferation of cancer cells. The researchers suggest that irregular food intake that causes cycles of fasting/eating may give cancer cells the ability to metastasize.

The mechanism of fasting and fasting-mimicking diet (FMD) was assessed in terms of the possibility of protecting the properly functioning cells from the toxic effect of chemotherapy. The fasting described in literature lasted from 12 hours to 3 weeks [11, 21]. In the study by *Brandhorst* et al. [11] introduction of two month-long cycles of FMD in mouse models caused elongation of their life, decrease in the amount of visceral adipose tissue and decrease in the incidence of cancer. The above diet: low in calories, low in protein, high in fats and rich in complex carbohydrates was related to obtaining an effect similar to the results obtained while applying fasting in healthy mice. It was observed that short-term fasting for 48 hours was an effective method of protecting the normal cells of mice from the toxic effect of chemotherapy. Introduction of fasting caused enhancement of the ability to react to chemotherapy applied against cancer cells of melanoma, glioma and breast cancer. In mice with neuroblastoma, cycles of fasting combined with chemotherapy and different methods of treatment caused longer survival with no progression of the cancer [46]. Similarly, in the study conducted by *Di Biase* et al. [21] it was observed that FMD cycles in combination with chemotherapy increased the effectiveness of anti-cancer treatment by stimulating the immue system. Discovering that the FMD cycles may increase the effectiveness of chemotherapy in terms of cancer cells, and, at the same time, limit this toxicity in mice interested the scientists. The above information was used in clinical studies. Currently, studies on the possibility of applying fasting in patients with prostate and breast cancer are in progress [27, 33, 70].

Due to the fact that in animal models evidence concerning the benefits of applied fasting was provided, the above mechanism was assessed in a group of 2413 women between the age of 27 and 70, at early stages of breast cancer. Night fasting that lasted on average 12,5 hours was applied. In the study it was observed that night fasting prolonged to more than 13 hours may be a simple, non-pharmacological strategy of reducing the risk of breast cancer relapse. The authors of the above study expressed an assumption according to which prolonged night fasting may potentially decrease the risk of type 2 diabetes, cardiovascular diseases and some cancers. However, randomized studies on the subject are needed [54].

In the study by *Safdie* et al. [69] 10 cases of patients with cancer, subjected to chemotherapy (7 women and 3 men) aged 44 to 78 with diagnosed breast, prostate, ovary, uterus, lung and esophagus cancer were analyzed. 48 to 140 hours-long fasting before chemotherapy and/or 5 to 56 hours-long fasting afterward chemotherapy was applied in patients. On the basis of observation of this group of patients the authors concluded that fasting in combination with chemotherapy was feasible and safe, and could reduce chemotherapy-induced side effects. The patients reported reduction of fatigue and weakness and less side effects from the digestive tract in comparison with the state of being before the application of fasting.

At Leiden University Medical Center (NCT01304251) 13 women at early stage of breast cancer were qualified and randomly assigned to a study in order to assess the safety of 24-hour-long fasting before and after applying chemotherapy. In the above pilot study it was confirmed that short-term fasting was well tolerated and safe, and it could limit hematological toxicity and increase protection from DNA damage in normal cells [18]. In addition, fasting could influence destruction of cancer cells by activating the immune system and/or enabling the immunological cells to recognize the cells of malignant cancers [11].

LOW-CARBOHYDRATE DIETS

According to the recommendations of the World Health Organization (WHO) carbohydrates should constitute 45-65% of daily caloric intake. It is related to the daily need of an organism for, among others, glucose as a source of energy. The brain, the erythrocytes, the leukocytes and the renal cortex are directly dependent on glucose. In the conditions of fasting tissues dependent on glucose may adapt to metabolism of fats. During the process of gluconeogenesis glucose may be produced in the liver and in kidneys from glucogenic amino acids, glycerol and lactate. While fasting, the organism may obtain up to 200g of glucose from the pathway described above. This amount is sufficient to satisfy the needs of glucose-dependent tissues [74, 90].

The *Atkins* diet

In the years 1972 - 2003 *Robert Atkins* [4] promoted low-carbohydrate diet as a method in obesity treatment. He recommended restricting carbohydrates to up to 30 g/day and increasing protein and fats intake - those could be consumed without limitation.

He divided this diet program into several phases. The first phase was essential due to ketosis induction in patient, and it lasted 14 days. Then, the share of energy from carbohydrates in the diet was increased by 10 g per week. The final element of the process was the maintenance phase. According to the author, the patient could consume fat-rich dairy products, eggs, meats, fish and vegetables, and, in further phases of the diet, also fruit and nuts.

Safety of applying modified *Atkins* diet in patients with diagnosed cancer was assessed. In the diet, carbohydrates were restricted to 20 to 40 grams per day. The energy value in the diet was not reduced. Due to the declining health of patients, unrelated to the diet, and due to personal reasons the applied dietary program was assessed in 11 out 17 qualified patients. In all the patients, loss of body weight was noted, yet the hematological, biochemical and lipid parameters remained stable. The survey data showed that the quality of life slightly improved. Scientists believe that modified *Atkins* diet was safe and feasible at advanced stage of cancer, yet, due to lack of results from other studies, the above issue requires further research [81].

Ketogenic diet

In 1921 Dr *Wilde*r from the Mayo Clinic proposed a diet that consisted in increasing the share of energy from fats, on the basis of biochemical processes of fasting. He was also one of the first people to use the term of ketogenic diet (KD). The above diet is applied with good results in treatment of drug-resistant epilepsy [5, 93]. During KD, oxidation of fatty acids occurs and ketone compounds - acetoacetate, β-hydroxybutyrate and acetone - are produced. When the concentration of ketone compounds in blood is equal to 4mmol/l they may be used as a source of energy by the central nervous system [24].

As early as in 1987 KD was also applied in cancers. *Tisdale* et al. [82] observed decrease in tumor mass and improvement in health (at the stage of cancer cachexia) in mice with colon cancer when KD was applied. In the research conducted by *Zhang* et al. [98] studies on the influence of KD on cancer cells depending on the expression of key enzymes of ketone compounds catabolism *in vivo* and *in vitro* were conducted. Activity of enzymes (3-hydroxybutyrate dehydrogenase, 1BDH1 and 3-oxoacid CoA transferase 1,OXCT1) responsible for catabolism of ketone compounds in vivo and in vitro, was studied in two representative cell lines (HeLa and PANC-1). It was proven that response to application of KD was present to a larger extent in cancer cell lines in which low activity of 1BDH and OXCT1 occurred. In meta-analysis published in 2016 by *Klement* et al. [41] 12 studies assessing survivability of mice with cancers in whom KD was applied were analyzed. The authors of the meta-analysis observed that application of KD in mice delayed tumor growth. The effect of the diet depended on the location of the tumor and the stage of advancement of cancer.

The evidence regarding the beneficial effect of KD in animal models was used in clinical studies in which application of ketogenic diet in terms of its safety and the possibility of its application was analyzed. KD was introduced in 16 patients with advanced cancer (among others: breast, ovary, esophagus, pancreas, colon, lung and stomach cancer). The therapy lasted for 3 months. In 6 patients there was an improvement in emotional well-being and in the quality of sleep [72]. Similar results were obtained by *Fine* et al. [23]. KD was applied in 10 patients for 26 to 28 weeks. Adverse effects were not noted and the diet was deemed possible to be applied in cancer patients. *Klement* et al. [42] also confirmed that introduction of KD during standard therapy was safe and did not cause adverse effects. Loss of body weight in patients was related to reduction of adipose tissue, not muscle tissue. Patients reported well-being on a diet in which carbohydrate intake was below 50 g. Tumor regression at early stages of the illness occurred as expected, however, in one patient progression of illness occurred, and it intensified after the end of KD.

Ketogenic diet and brain glioma

In the recent years, studies on the relationship between KD and the nervous system-related cancers have been commenced. Malignant gliomas have been occurring increasingly within the last 30 years, especially in elderly people. Prognosis for patients with gliblastoma multiforme (GBM) is bad, and the survival median is equal to 12 months [35]. Due to bad prognosis and ineffectiveness of the available treatment methods, new therapeutic methods are being sought for [13]. It has, moreover, been observed that hyperglycemia is related to worse prognosis in patients with GBM [57].

In 1995, on the basis of a study of two cases of pediatric patients with brain cancers (astrocytoma) at an advanced stage of the illness, the KD model with 60% of energy share from medium-chain fatty acids was incorporated. The remaining macronutrients were distributed in the following way: 20% of energy share from proteins, 10% from carbohydrates and 10% from the remaining fats. In the area where the tumor was located glucose uptake was measured using positron-emission tomography. After 7 days of the diet being applied by both patients, reduction of glucose uptake equal to 28,7% was noticed in the area of the tumor. In one of the patients significant clinical improvement in terms of mood and development of new skills were observed. During continuation of KD for 12 months no progression of illness was observed [63].

The other case description concerned a 65 years old female patient, in whom glioblastoma multiforme was diagnosed. After surgical resection of GBM ketogenic diet was also incorporated into the standard therapy in this case, using 4:1 ratio (4 grams of fats to 1 gram of carbohydrates and protein altogether). The daily calorie intake was established at the level of 600 kcal. The patient's body mass decreased by about 20% after two months of KD implementation, and no presence of brain cancer cells was detected. Strict diet was continued for 6 months. 2 months after the end of it, relapse of the illness was detected in the image of magnetic resonance [99].

Champ et al. [13] applied KD in 6 patients with GBM during chemotherapy and radiotherapy. The implemented diet was well tolerated, and no episodes of hypoglycemia were observed in patients. Four patients survived; the observation time median was 14 months. However, as the authors of the study state, the benefits of KD incorporation remain dubious.

In the ERGO study (NCT00575146) the possibility of applying KD (60 g of carbohydrates per day) in 20 patients with recurrent glioma 3 months after the end of radiotherapy was assessed. The diet consisted of, among others, fermented milk beverages (500 ml) and plant oils. The dietary model did not encompass calorie restriction, the patients were instructed which products they were allowed to consume. The implemented diet complemented the applied treatment. The average survival time with no progression of illness was 5 weeks, and the survival median - 32 weeks. The authors emphasized that the limited number of patients, lack of control group in the study and no randomization do not allow for unambiguous estimation of the KD effectiveness [67].

DIET MODIFICATIONS IN BREAST CANCER PREVENTION

The available research on the potential role of the KD in prevention of breast cancer and support of its treatment is based on the analysis of singular cases. There are no randomized clinical studies. Nonetheless, a relationship between high body mass index (BMI) and the incidence of breast cancer among women pre- and post-menopause has been observed. Body mass reduction was proposed as a potential goal reducing the risk of breast cancer; KD may be probably used to obtain this result [7, 38].

In 86 621 participants of the Nurses' Health Study (NHS) the relationship between implementing the DASH diet (*Dietary Approaches to Stop Hypertension*), diets with lower content of carbohydrates (based on plant-based products, animal products and general) and the risk of breast cancer after menopause was assessed. The DASH diet and the plant-based diet with limited amounts of carbohydrates (the median of carbohydrate content in the diet was 52,9%) was related to lower risk of breast cancer with negative estrogen receptors [25].

In the study conducted by The Finnish Social Institution's Mobile Clinic Health Survey (FSIIMCHS) the relationship between the content of fats in diet and later risk of breast cancer was studied in a group of 3988 women, aged 20 - 69. The authors of the study suggest that occurrence of breast cancer in patients was related to higher energy value in their diets, but not to complete share of energy from fats in the diet [44].

In a prospective cohort study, conducted on the basis of the data from The Canadian National Breast Screening Study (NBSS), the risk of occurrence of breast cancer depending on the glycemic index (GI) and the glycemic load (GL) was assessed in 49 613 Canadian women. In the above study, the GL in the analyzed diets was not related to the risk of breast cancer in particular subgroups, whereas the GI in the diets was related to higher risk of breast cancer in women post-menopause. The GI considers the quality of the consumed carbohydrates along with the product, and the GL additionally considers their amount. According to the authors, the participants of the study in whom cancer occurred could have consumed a wider variety of products with high glycemic index that were also characterized by worse quality of carbohydrates [76].

DIET MODIFICATIONS AND HEAD AND NECK CANCERS

Due to their similar etiopathogenesis, pathomorphology and clinical course, cancers located in the area of head and neck (HNC) are qualified into one group. Inflammations in the area of mouth cavity before occurrence of HNC and during cancer were observed more often in diabetic patients. Therefore, studies including appropriate nutritional support were undertaken [85, 88].

In a randomized prospective study, using double-blind test, standard enteral nutrition and enteral nutrition specific for the illness containing eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA) were administered in 111 patients with HNC undergoing chemotherapy. Improvement in the nutritional condition and in functioning during chemotherapy was observed in patients in whom feeding model rich in EPA and DHA fatty acids was applied [22].

Patients at advanced stages of head and neck squamous cell carcinoma (HNSCC), treated post-surgically, were qualified for the first phase of the clinical trial. For 5 weeks, the patients underwent chemotherapy with simultaneously incorporated KD, with adequate parameters being monitored. The

average observation time of all the included patients (n=9) from the moment chemotherapy ended was 7,1 month. Out of 9 qualified persons, 3 managed to apply KD for 5 weeks [3]. The foods were administered in the form of cocktails via percutaneous endoscopic gastrostomy (PEG), or were administered orally, depending on patient's capability. Discontinuation of application of KD was related to nausea (3 patients), fatigue (1 patient), hyperruricemia (1 patient) and additional stress for patients, related to following the diet (1 patient).

The paleo diet

The paleo diet is also considered to be a low-carbohydrate diet. The concept of this diet is to follow the way of eating that is based on eating habits of our ancestors from the Paleolithic era. The ancestors consumed foods that were gathered or hunted by them on their own. In compliance with the description of low-carbohydrate diets, paleo diet is dominated by proteins and fats from meat products, fish, eggs, vegetables and nuts. Supply of carbohydrates in the diet is not specified unambiguously. Eating fruit and selected starch vegetables is permitted. As authors of the study indicate, the paleolithic diet may be used as eating strategy for weight loss [64]. *Whalen* et al. [92] conducted an analysis of two exemplary diets: the paleolithic diet and the Mediterranean diet, the health-promoting effects of which are supported by studies [73]. Consumption of products in accordance with the above diets was verified using the Food Frequency Questionnaire (FFQ). The paleolithic diet that was analyzed in the study consisted of higher supply of vegetables, fruit, lean meat, fish, nuts and low supply of red and processed meat, sodium-rich products, dairy and wholegrain products, sweetened beverages, alcohol. Lower mortality rate of all causes was observed in people who conformed with the paleolithic or the Mediterranean diet. Additionally, decrease in dynamic of oxidative stress and mortality caused by cancers, mostly by colon cancer, was observed in the patients. As the researchers emphasize, it was the first study that analyzed the aforementioned dependencies [92].

Considering the arguments advocating application of KD and the paleolithic diet, the researchers developed a dietary model that is known as the paleolithic ketogenic diet [83, 84]. The paleolithic ketogenic diet was introduced in a 60 years old patient, diagnosed with epithelial-myoepithelial carcinoma of the parotid gland, who did not agree to conventional treatment. Diet consisting mainly of meat and fats was suggested. The ratio of the mass of fats to the mass of protein in the diet was 2:1. The amount of plant products in the diet was less than 30% of all consumed foods. No calorie restriction was applied. The patient did not report adverse effects and his state of being and physical fitness improved. It can be concluded from the data that introduction of an alternative dietary model inhibited tumor growth. The patient continued the diet for 20 months [83].

In another case description, the authors assessed introduction of the paleolithic ketogenic diet in a 62 years old patient diagnosed with rectal cancer. Radiotherapy combined with the diet was applied in the patient for 6 weeks. Later on, the diet itself constituted independent therapy. Grains, milk, dairy products, oil plant seeds, legume seeds, plant oils, including coconut oil and olive oil, were eliminated from the diet. Vegetables constituted less than 30% of the entire daily range of foods. They were mostly root vegetables. The patient continued the diet for 24 months. Tumor growth was inhibited within the first 5 months when the patient strictly complied with the diet, which could be related to the simultaneously applied radiotherapy. Symptoms suggesting progression of the illness were noted when the patient did not comply with the dietary recommendations strictly. An operation within 24 months revealed metastases to liver. According to the authors, rectum operation was delayed by two years because of the influence of the diet [84].

ADVERSE EFFECTS OF LOW-CARBOHYDRATE DIETS

In most studies concerning KD negative effects such as: occurrence of kidney stones, decreased weight gain and deficiencies of mineral substances were observed when the diet was applied for 1 - 6 years [9, 71]. In the literature the following are described as the adverse effects: torpor, nausea and vomiting caused by intolerance of the diet, especially in children. In addition, children may be prone to develop hypoglycemia due to low amounts of carbohydrates in the diet. In adults, on the other hand, gastrointestinal discomfort related to high amount of fats in diet and constipation were noted [20]. In a prospective pilot study it was observed that the level of LDL cholesterol in blood serum was elevated after one year if KD was complied with [62]. *Hayashi* et al. [29] monitored the level of selenium, zinc and copper in patients' blood serum and their daily consumption both before and 6 months after the beginning of KD. Due to the occurring deficiencies during the diet, the authors of the study suggest supplementation with these mineral substances.

There is a risk of kidney damage caused by nitrogenous waste products excretion. The authors do not demonstrate definite certainty of the occurrence of KD-related kidney damage, but in 6% of children kidney stones were noted while applying the diet for 1 - 5 years [71]. Introduction of KD may be related to occurrence of elevated concentration of ketone

compounds in blood which is in particular undesired in the case of patients with diabetes in whom there is an increased risk of ketoacidosis - a state that is potentially life-threatening. However, the concentration of ketone compounds and glucose in blood of most adult patients was not elevated [72]. Adaptation of patient's organism related to changing the standard diet to low-carbohydrate diet may be accompanied by: constipation, headache, halitosis, muscle contractions, general weakness, rash, diarrhea. Constipation and digestive tract dysfunctions may result from smaller volume of food, increased share of fats and decreased supply of fiber in the diet [39, 96].

Xia et al. [95] showed that application of KD may result in occurrence of cancer mutations. Elevation of acetoacetate concentration in blood serum led to growth of human melanoma in mouse models. These observations indicate pathological relationships between nutrients and specific oncogenic mutations that occur in human cancers. Selective influence of fat in diet on the increase of proliferation of tumor cancer cells (BRAF V600E) took place via elevated ketogenesis.

According to the Polish standards for nutritional therapy, fasting should not be applied in order to inhibit tumor growth. It can moreover significantly worsen the state of a patient in the course of cachexia, leading to his or her faster death. Combining the above alternative methods is therefore not recommended until there is adequate evidence that confirms their effectiveness [43].

CONCLUSIONS

Despite the progress in anti-cancer treatment, prognosis for many cancer patients is bad, and most current methods of treatment are limited due to occurring adverse effects. Alternative dietary interventions seem to be a method of cancer patient support that is possible to be applied, yet, due to their restrictive form, they may not be tolerated by patients. The authors of the studies emphasize that limited number of patients, lack of control groups and lack of randomization do not allow for unambiguous estimation of the effectiveness of fasting and low-carbohydrate diets.

The mechanism of KD in combination with standard treatment has not been fully explained. In preliminary studies it was demonstrated that patients who were able to continue low-carbohydrate diets showed: improvement in health, decrease in tumor mass or its slower growth. Molecular mechanisms of the diet-cancer mutation relationship are unclear. Introduction of fasting may sensitize cancer cells to chemotherapy and lead to re-directing energy toward conservation and repair of normal cells. On the other hand, fasting may also increase autophagy regulation and, according to the literature, its mechanism may have two-way activity, hence further studies are needed.

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