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Is it Possible to Use the Ketogenic Diet to Treat Cancer Patients?

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Editorial

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Introduction

Cancer cells have a particular metabolism, which differs from normal cells; according to the so called "Warburg effect", cancer cells have a predominant use of anaerobic glycolysis, i.e. they are able to use the sugar (glucose) present in the blood in any condition, both in the presence and absence of oxygen. This characteristic explains the great need that the cancer cells have for sugar, in order to rapidly duplicate and use mainly glucose as an energy source. Precisely for this reason, in PET, a diagnostic technique used to visualize the tumor mass, a glucose analogue is used as a tracer [1-5]. A diet that allows keeping low blood sugar level could therefore be useful in limiting the nourishment of cancer cells as much as possible. In conditions of low circulating glucose levels ketosis, that is the metabolic pathway that leads to the production of ketone bodies, is induced. In this way the cancer cells are "starved", while normal cells adapt their metabolism to use ketone bodies as an alternative energy source to survive. In addition, as blood glucose levels decrease, insulin and insulin-like growth factor levels, which are important factors in the proliferation of cancer cells, decrease accordingly. For this reason, clinical studies in the oncology field in recent years have focused mainly on Low-Carb diets, and in particular on the Ketogenic Diet. Recent research shows that the ketogenic diet has a potentially limiting effect on tumor growth, it could protect healthy cells from damage from chemotherapy or radiation, also accelerating chemotherapy toxicity against cancer cells and reducing the degree of general body inflammation. The ketogenic is not a high-protein diet, it is actually a norm-protein one, high in fat and low in carbohydrates, born in the 1920s for the treatment of drug- resistant epilepsy, but today it is applied also for other diseases, including obesity, insulin resistance and cancer. The ketogenic approach mimics the metabolic effects of fasting, as in the absence of sugars the body produces ketone bodies even in case of prolonged fasting. In the classic ketogenic diet, fats reach high quantities, even up to 90% of the total daily energy, 8% is represented by proteins and only 2% by sugars, with a 4: 1 ratio of fats to proteins + carbohydrates. There are also alternative ketogenic protocols that make adherence to the diet much easier, but the total amount of carbohydrates in this case must never exceed 50g per day.

Therefore, in the ketogenic protocol, food with high carbohydrate content is limited and high content of good fats (mainly of vegetable origin) is instead preferred.

Specifically, the recommended foods are:

- Fish products, meat and eggs
- Some types of cheeses / dairy products
- Dried fruit in seeds (walnuts, almonds, pistachios, etc.) and seasoning oils (especially extra virgin olive oil)
- Vegetables (with the exception of some with a higher sugar content such as tomatoes, pumpkin and carrots)

The foods not recommended, on the other hand, are:

- Cereals, potatoes and derivatives
- Legumes
- Fresh fruit (except some low-carb fruit such as blackberries, raspberries, blueberries and strawberries)
- Sugared or sweetened drinks, various sweets, beer and spirits, industrial products, etc.

Clinical studies show that even if it is a diet with a high fat content, the ketogenic diet does not lead to an imbalance of blood chemistry parameters, but rather determines an improvement, in particular in the levels of total cholesterol, LDL ("bad cholesterol"), triglycerides, blood glucose, as well

as a significant reduction in weight and consequently in the body mass index, an important consequence especially in patients who are in a condition of excess malnutrition. Clearly, it is important to monitor weight loss in patients who, on the other hand, have a defect of malnutrition and therefore risk damage related to excessive weight loss and cachexia. Regarding the correlation between ketogenic diet and tumors, the primary outcomes considered are tumor size or survival; secondary outcomes concern changes in vascularity, glucose uptake at the tumor site, changes in gene expression and metabolic parameters. However, the effectiveness of this nutritional protocol could be influenced by various factors, such as the type of tumor, the genetic background or the side effects of the disease and / or therapy [6-9]. There are currently no randomized controlled trials with a large cohort of patients, but none of the clinical studies conducted so far have reported serious adverse events or toxicities related to the ketogenic diet, supporting the possible implementation of protocols of this type. The ketogenic diet creates a very adverse environment for the proliferation of cancer cells and therefore could represent an adjuvant in the specific treatment of the cancer patient. The effectiveness of the ketogenic diet has been significantly studied and confirmed for different types of cancer, but in particular for neuroblastoma and glioblastoma among brain tumors, and also for prostate, colon, pancreas and lung cancers. Given the particularity of the type of treatment and the fragility of the patients to whom this dietary regimen is proposed, it is important to remember that seeking advice of a professional expert in nutrition is essential, to prevent imbalances or nutritional deficiencies. Moreover, this protocol cannot be feasible in some specific pathological conditions.

Ketogenic Diet and Fasting - Possible Therapeutic Effects

In addition to the ketogenic diet, a new approach tested recently in cancer patients is the Fasting- mimicking Diet (DMD); as already mentioned, fasting, like ketosis, leads to large alterations in growth factors and metabolite levels, generating environments that can reduce the ability of cancer cells to proliferate and thus improve the effects of anticancer therapies. Additionally, fasting or mimicking fasting increases the resistance of normal non-cancerous cells to chemotherapy and promotes regeneration in normal tissues, which could help prevent side effects of treatments. Prolonged fasting is hardly tolerated by patients, but fasting-mimicking cycles may be more manageable and well tolerated. Several clinical trials combine the fasting-mimicking diet with chemotherapy, immunotherapy or other therapeutic strategies to increase the effectiveness of the treatment and reduce side effects, such as fatigue, neutropenia and cardiac myopathy, in order to improve the patient's quality of life. When the metabolic pathways of fasting are activated, normal cells are protected from the effects of chemotherapy or other anticancer therapies, while cancer cells become more sensitive. Probably the key mechanism by which fasting increases drug tolerability is related to the regulation of insulin-like growth factor IGF1. While cancer cells are able to adapt to limited concentrations of oxygen and nutrients, many types of cancer cells are unable to make changes that would allow them to survive in the nutrient-deficient and toxic environment generated by the combination of fasting and chemotherapy. The Fasting-based dietary approaches that have been studied more extensively in oncology include actual fasting, that is, abstinence from all food and beverage except water, and mimic fasting. Clinical data indicate that fasting for at least 48 hours may be required to achieve clinically significant effects, such as preventing chemotherapy-induced DNA damage to healthy tissues and helping to maintain the patient's quality of life during chemotherapy [7,9]. However, most patients refuse to do so or have difficulty completing total fasting, and the potential risks of prolonged calorie and micronutrient deficiency associated with it are difficult to manage. This is why today we talk more about mima-fasting, that is dietary regimes designed with a very low calorie content (starting from a minimum of 300 kcal up to a maximum of 1,100 kcal per day), low intake of sugars and proteins, which recreate many of the effects of water fasting but with better patient compliance and a reduced risk of nutritional deficiencies. During a fasting-mimicking diet, patients generally receive unlimited quantities of water, small standardized portions of vegetable broths, soups, juices, dried fruit bars and herbal teas, with the support of micronutrient supplementation. The regenerative effects of fasting and mime-fasting seem to be maximized by the transition from the "hunger response" mode to the refeeding period, in which cells are more prone to "rebuilding". Since the ketogenic diet doesn't involve total fasting, it doesn't have the same kind of "regenerating" effect. Fasting-mimicking diet cycles are more feasible than chronic fasting diets because they allow patients to consume food, maintain a normal diet between cycles, so they do not result in severe weight loss and possible harmful side effects on immune and endocrine systems. Since the fasting-mimicking diet can be a more manageable and useful protocol in order to have a real decrease in IGF1, visceral fat and cardiovascular risk factors, it could be a valid dietary approach to be carried out in cycles also for the primary prevention of chronic diseases in general. However, it is important to emphasize once again that frail, malnourished or patients at risk of malnutrition should not be enrolled in fasting or mimicking clinical trials and the patient's nutritional status and / or anorexia should be carefully monitored during these trials. An adequate intake of proteins, essential fatty acids, vitamins and minerals combined, where possible, with light and / or moderate physical activity aimed at increasing muscle mass

should be applied between fasting or mimicking-fasting cycles, so that patients can maintain a good percentage of lean mass. Some studies have shown a reduction in chemotherapy toxicity in patients who fasted from 24 hours before therapy to 24 hours after. Fasting also appears to reduce the typical side effects of chemotherapy, such as nausea, vomiting, diarrhea, abdominal pain, and mucositis. Fasting could reduce the ability of cancer cells to survive and adapt, making them more susceptible to chemotherapy and it seems to increase the ability of normal cells to resist chemotherapy treatments and promote normal tissue regeneration through mechanisms that involve the metabolic pathways of stress response, autophagy, decreasing the insulin-like growth factor (IGF-1), so that cell growth and proliferation is downregulated. Initially it was proposed that the improvement in the efficacy of chemotherapy induced by fasting needed to be mediated in part by the reduction of IGF1 and blood glucose levels. However, it was found in a recent study that fasting-mediated enhancement of endocrine therapy activity in hormone receptor- positive breast cancer (HR + breast cancer) also relies on the ability of fasting to reduce circulating insulin and leptin concentrations. On the other hand, it has been shown that the effects on the reduction of IGF1 and the hypoglycemic capacity of fasting are fundamental for the reduction of the toxicity of chemotherapeutics. Levels of leptin and IGF1 remain lower than those found at baseline until two to three weeks after the end of the fasting-mimicking period; this indicates that some metabolic effects of fasting-mimicking can persist even for long periods, possibly contributing to creating unfavorable conditions for tumor growth not only at the time of the disease in progress, but also in the longer term.

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