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The ketogenic diet–defining a role in cancer therapy

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Cancer cell metabolism

Cancer cells grow without boundaries and proliferate at high rates. Therefore, they require large amounts of energy. Unlike normal cells, cancer cells preferentially feed on glucose as a result of an overactive glycolytic process. While normal cells go through the process of glycolysis, the citric acid cycle, and the electron transport chain, cancer cells don't. Instead they favor glycolysis over oxidative phosphorylation even in the presence of oxygen. This is a phenomenon known as the "Warburg effect," which is seen even before the onset of hypoxia [1,2]. Proponents of the metabolic theory of cancer propose that defects in glycolytic enzymes as well as ketolytic enzymes within the mitochondria could be responsible for this effect.

Other scientists describe the origin of cancer as lying not within the cell but rather in the surrounding stroma, where cancer-associated fibroblasts also exhibit aerobic glycolysis [3]. These fibroblasts secrete hydrogen peroxide, which triggers oxidative stress. This stress transfers over to adjacent fibroblasts, which in turn boosts more aerobic glycolysis. The fibroblasts also produce lactate and ketones and transfer this energy to adjacent cancer cells. What we see as being visible on PET CT scanning with Fluoro-2-deoxy-D-glucose (F-2-DG), are actually cells of the tumor stroma rather than that of the cancer cell itself [3]. This energy transfer is what we call the "reverse Warburg effect."

Regardless of the location, there is increased lactic acid production, which tilts the tumor microenvironment towards a lower pH. This acidic microenvironment can blunt the innate immune response towards cancer, accelerate tumor growth and promote cancer metastasis [4-6].

Weight gain and cancer

Cancer patients are commonly perceived to be in a constant catabolic state. As time progresses, weight loss accelerates, and cachexia develops despite aggressive caloric supplementation. This is a hallmark of terminal cancer. Weight loss is perceived as a harbinger of disease progression, and measures to thwart this process are often encouraged. Consequently, in oncology clinics there is a push to increase patients' caloric and carbohydrate intake in hopes of energizing the body to maximize its chances in the fight against cancer. In reality, there is little scientific data to support this approach. In fact, there is growing evidence that excessive weight gain may be in fact deleterious to cancer patients [7-9].

Obesity is linked to increased cancer incidence [8,9]. One reason behind this is a blunted body response to leptin. Leptin is a proinflammatory, appetite-decreasing hormone that arises from fatty tissue. Obese patients will eventually develop high leptin levels but later become unable to respond to its anorexic effects, hence becoming leptin resistant. They encounter difficulty in losing weight despite having high levels of leptin. Hyperleptinemia is seen in many cancers [10-13]. Leptin can promote cancer by activating cancer stem cell division. It increases expression of nuclear factor kappa B/hypoxia inducible factor alpha (NFκB /HIF-1α) and vascular endothelial growth factor (VEGF), which stimulates new blood vessel formation (angiogenesis), cell proliferation and inhibition of apoptosis. Indeed, targeting leptin signaling may be an attractive option for targeted cancer therapy [14].

Hyperinsulinemia is associated with obesity [15-17]. High carbohydrate consumers actively produce insulin in response to high blood glucose. Insulin allows glucose to enter cells where they can be converted into energy. There is more insulin receptor binding, which promotes mammalian target of rapamycin (mTOR) signaling, tumor growth and invasion. Over time, obese patients become insulin resistant and the resulting hyperinsulinemia can likewise be cancer promoting [10,11]. Carbohydrate-restricted diets can be of benefit by lowering blood glucose and decreasing insulin receptor binding.

High carbohydrate, nutrient poor diets can result in unhealthy weight gain and fuel cancer growth. A high fat, ketogenic diet could paradoxically reverse cancer associated cachexia. Tisdale et al found that a high fat diet could promote weight gain by increasing carcass mass and could reduce tumor size in a mouse model of colon cancer [18].

Cancer epigenetics and the role of a ketogenic diet

Tumor suppressors like p53 are highly mutated and hyper-acetylated in many human tumors, enabling them to escape proteasome induced destruction, promote oncogene expression and develop resistance to chemotherapy [19]. Low-carbohydrate dieting can also down-regulate p53 mutants via de-acetylation and induce cell death. This blunting of mutant p53 expression, increases lifespan [20].

Ketogenesis occurs when the body produces ketones in response to fasting, starvation, or dietary carbohydrate restriction. By adopting a ketogenic diet, one slows down cancer growth via inhibition of IGF, PI3k/AKT/mTOR signaling pathways. Ketones by themselves can cause epigenetic changes that can synergize with existing cancer therapeutics [21-24].

Current data on humans and cancer are still very preliminary, consisting of mostly safety studies and case series [25-29]. Although efficacy in cancer cannot yet be determined, the existing body of evidence suggests that it is safe to follow. Given the expected lifespan

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of advanced cancer patients, it is unlikely that long-term serious effects will be of issue. However, by itself, it is unlikely that the ketogenic diet can be used as a primary therapy against cancer. There might be more benefit for it as an adjunct to standard treatment such as biologics, targeted therapies or conventional chemotherapy [30].

Future directions

Targeted therapies are slowly populating the oncologic landscape. Immunohistochemical staining of ketolytic and glycolytic enzymes as well as identification of biomarkers (leptin and insulin) could be useful in the future. A ketogenic diet in addition to standard chemotherapy and/or radiation may improve tumor control and treatment outcomes, including quality of life. Increasing acceptance of this novel approach to cancer nutrition could hopefully define a new paradigm in cancer care.

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