



International Journal of Case Reports & Short Reviews

Case Report

Ketogenic Diets - Potential Role in Cancer Management - 3

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Submitted: 01 May, 2016; **Approved:** 07 June, 2016; **Published:** 08 June, 2016

Citation this article: Tan-Shalaby J. Ketogenic Diets - Potential Role in Cancer Management. Int J Case Rep Short Rev. 2016;2(1): 001-003.

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ABSTRACT

Existing dietary cancer guidelines focus on maintenance of body weight during cancer treatment. In most cases, there is a push to encourage increased caloric intake, supposedly to counteract the expected weight loss that occurs during cancer treatment. It is perceived that the chemotherapy and/or radiotherapy will increase weight loss in an already catabolic state, and by increasing caloric intake one might somehow maintain health and improve resistance to infection. For years, nutritionists advise patients to increase their caloric food intake and to gain more weight. Despite the strong push, little firm evidence exists to support this way of thinking. There is emerging evidence that dietary changes contrary to this approach can significantly affect cancer growth and metastases.

The genetic theory of carcinogenesis claims that cancers are initiated by specific unique mutations. The race to find the drug that matches these identified mutations is based on the belief that by doing so, the cancer will be cured. Despite a few durable successes [1], the majority of advanced cancers are not cured, and the improvement in lifespan from most newly developed drugs, is often measurable in months. Obviously we have not unlocked the cure for cancer despite the rapid progress in identifying scores of genetic mutations unique to various tumors. Many times we have identified the targeted pathway but the chosen targeted therapy fails to deliver lasting results. Perhaps other untouched pathways exist by which the tumor finds a way to survive? There is much discussion on crosstalk between signaling pathways and their role in tumor survival [2-4]. In recent years, metabolic theories underlying carcinogenesis have attracted renewed attention.

Tumors preferentially use glucose and are unable to use fatty acids and protein as a major source of energy. As a result there is dependence on glycolysis. Cancer cells produce excess lactic acid by way of this upregulated glycolysis. Aside from being an indicator of excess glycolysis, lactic acid also regulates redox homeostasis, promotes angiogenesis and tumor growth [5]. Lactic acidosis leads to a proportionately acidic microenvironment that not only facilitates metastases, but also suppresses the anti-cancer immune response and enables cancers to escape immune related destruction [6].

Glucose and carbohydrates stimulate insulin signaling which leads to insulin receptor binding and subsequently, stimulation of mitogen-activated protein (MAP) kinase and phosphatidylinositol-3-kinase PI3K pathways. Insulin ligands such as insulin growth factor IGF-1 and IGF-2 also bind to their own receptors which lead to increased signaling of the mammalian target of rapamycin (mTOR) and Ras/Raf/mitogen-activated protein kinase/extracellular signal regulated kinase ERK pathways [7,8]. Ultimately this results in increased tumor growth, invasion and metastases. By decreasing glucose and carbohydrate intake, the resulting drop in insulin levels inhibits not only mTOR, phosphoinositide-3-kinase PI3K, and ERK signaling, but downstream of these pathways including hypoxia inducible factor HIF-1 α , vascular endothelial growth factor VEGF, and adenosine monophosphate-activated protein kinase AMPK, all of which are currently popular pharmacologic mechanisms of targeted drugs such as bevacizumab, sirolimus, and idelalisib.

Inflammation can increase our risk of developing cancer. Tumor signaling as a result of unbridled inflammation is well described [9-11]. Obesity is linked to many cancers. Obese individuals often have insulin resistance as well as a blunted leptin response. Consequently they have high levels of insulin and leptin, both of which lead to a pro-inflammatory state [12-16]. The ketogenic diet was found to have direct anti-inflammatory effects [17,18]. Will dietary changes

that decrease inflammation, and targeting multiple pathways make a more global impact on tumor signaling inhibition?

Caloric restriction, without malnutrition is well known to prolong the lifespan of diverse species [19,20]. Previous in-vitro and animal studies support this inhibitory effect of carbohydrate restriction on cancer growth [17,21]. Several human case studies and safety studies have completed or are currently in progress [7,22-25]. Ketosis as a result of carbohydrate restriction and exogenous ketone supplementation also have direct anti cancer effects [26]. Fine et al found an association between the degree of ketosis and 18F-2-fluoro-2-deoxyglucose tumor uptake as measured by positron emission tomography (PET). Tumor progression had significantly lower relative increases of β -hydroxybutyrate in patients whose tumors progressed at one month compared those with stable or responsive disease by metabolic activity on PET scans. Schmidt et al found that the ketogenic diet was safe even for very advanced cancer patients [27].

The ketogenic diet appears to be safe in cancer patients but can we combine it with chemotherapy or targeted therapies? Can we identify diet-responsive patients using mitochondrial biomarkers such as transketolase TKL, succinyl-CoA and insulin growth factor binding proteins? [28-31] Can existing activating protein mutations that will predict for non-response to dietary intervention? Whether this is effective in cases of tumors with metastatic brain lesions where chemotherapy is expected to have poor blood-brain barrier penetration is unknown. There is great potential in boosting these dietary changes in combination with targeted chemotherapy and improving the response rates and survival of many cancers. More studies are urgently needed.

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