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The Ketogenic Diet and Cancer

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Abstract

Cancer is considered one of the greatest killers in the developed world. Researchers are actively looking for treatments to better the prognosis of the disease. We present herein a dietary modification capable of modifying cancer growth and metabolism, the ketogenic diet (KD). The ketogenic diet is very low in carbohydrates, the main energy substrate for cancerous cells, which lose their ability to utilize alternative fuel sources and mainly use glycolytic fermentation as their main energy source. It has been demonstrated that by severely limiting glucose availability and lowering circulating insulin levels which also lowers IGF-1, TNF, MTR (known growth factors),cancer growth can be slowed down and mean survival time extended, both in animal and human studies, as well as improving the quality of life (QoL). The Ketogenic Diet is proving beneficial to limit malignant tumor growth, however when combined with other therapies such as Hyperbaric Oxygen Therapy (HBOT) and Intravenous Vitamin C (IVC) seems to further potentiate this action.

Keywords: *Ketogenic Diet, Keto Diet, nutrition, cancer, cancer therapy*

Introduction

This literature review intends to state the severity of the Cancer epidemic, give an overview of the changes that occur within cancerous cells compare to healthy cells and how these metabolic changes can be used to target cancer cells while sparring healthy cells. We also explainhow a Ketogenic Diet (KD) might be therapeutic against cancer.

Cancer is amongst the top three causes of death in the developed world,both in the US and in Puerto Rico. In 2014,591,699 people died of malignanttumors in the US, only 25,000 (1) and in 2012 cancer killed more people in Puerto Rico than heart disease, averaging 5,439 people per 100 thousand inhabitants; to 5,089 for heart disease (2).Even though earlier detection of cancer has progressed the amount of deaths per year of cancer has barely changed in the last 50 years, while improvement in the treatment of Heart Disease has been significant, thus closing the gap between these 2 main killers (3). This could be considered a treatmentsetback, due to lack of progress against this degenerative disease, as the standard of care seems in the need of new and effective treatment options to improve the prognosis against cancer. For this reason,recent studies have been directed into the metabolic aspects of cancer. The idea of treating cancer as a metabolic disease instead of a genetic one is appealing. This is due to the fact that research has not been able to find a specific genetic cause, but has found at least seven metabolic differences between cancerous and normal healthy cells(4):

1. A shift from respiratory (aerobic) pathways as a main ATP production mechanism to fermentative (anaerobic) pathways (Oxidative phosphorylation to Fermentation).
2. Mitochondrial dysfunction; both in structure and function, as mitochondrialose their cristae and membrane potential, thus diminishing their energy production potential. Creating what has been named as ghost mitochondria.
3. Increased glycolysis, which raises lactic acid production thus lowering pH levels and oxygen transport efficiency.

4. Formation of coagulated proteins around cancerous cells, which shield these from the host immunological response (Cellular and humoral).
5. Augmented and uncontrolled cellular replication.
6. Loss of communication between cells.
7. Metastasis or colonization of other tissues by transformed cells.

These changes make cancer cells regress to resemble simple single organisms which use fermentation as their sole mechanism of ATP production. In the embryonic stage, undifferentiated embryonic cells are basically anaerobic and utilize the sugar of the ova for its ATP production needs. Embryonic cells replicate rapidly without differentiating. Some studies have tried with to reactivate the function of the mitochondria using dichloroacetate (DCA), which by inhibits PDK (pyruvate dehydrogenase kinase), decreasing the conversion of pyruvate to lactate, thus mobilizing pyruvate into the mitochondria and promoting respiration over fermentation(5). This mechanism may also reverse the suppressed mitochondrial apoptosis (programed cell death) in cancer cells, by increasing certain signaling ROS (Reactive Oxygen Species) and pro-apoptotic factors from the mitochondria.This has shown to reduce cancer growth in vivo in animal models.In addition, large doses of Vitamin Cmay assist in the transport of oxidation potential to the mitochondria therefore encouraging the utilization of the mitochondrial respiratory chain, encouraging differentiation, along with all of its' anti-carcinogenic mechanisms and implications (increase H2O2, collagen, humoral and cellular immune response) (6). Asascorbate's transport into the cell is facilitated by ascorbate's similar molecular structure to glucose and malignant cells have anincreased need for glucose; this could make for avery effective therapeutic approach.

Discussion

The increased dependency of cancer cells for glucose has been used as a diagnostic way of scanning for cancer using 18F-2-fluoro-2-deoxyglucose (FDG) which gives a positive positron emission tomographic (PET) result for areas consuming excess glucose.As a therapeutic option the limitation of glucose by consuming a diet very low in carbohydrates makes sense. This approach should limit the availability of energy substrate for the cancer cells while not affecting the availability of energy for normal healthy cells. Normal cells maintain their metabolic flexibility to utilize other sources such as ketones as energy while malignant cells lose this ability (7). This strategy should theoretically not only reduce the speed of replication of malignant cells by reducing available substrate, but also downregulate some of the growth factors associated with cancer growth, such as IGF-1 (Insulin like Growth Factor), TNF(Tumor Necrosis Factor) and MTOR (Mammalian Target of Rapamycin) as all of these decrease as insulin levels do; as well as activate apoptotic mechanisms that might eradicate these malignant cells(8). To attain these effects glucose levels must be extremely low in order to elevate ketone bodies for optimal therapeutic benefits, both of which can be achieved with a ketogenic diet (KD).

AKD is one which raises the level of Beta-Hydroxy butyrate (BHB) to over 0.5 Mmol/L, but for this to happen levels of insulin have to be suppressed for extended periods of time to allow for the body to utilize fatty acids as energy source and the liver to produce ketone bodies (9). This metabolic action is suppressed by the presence of insulin. When dietary carbohydrates are consumed the body releases insulin to lower blood glucose level and make it available to the cell, but the insulin surge needed to accomplish this inhibits fat utilization as energy. For this reason, a ketogenic diet must be high in fat (3:1 to 4:1, fat calories to protein and carbohydrates), moderate in protein and very low in carbohydrates. Most people think of the Atkins diet when they think of a low carbohydrate diet but the Atkins diet is not ketogenic due to its' unrestricted protein intake, which would raise blood glucose levels by gluconeogenesis, primarily by means of glutamine and produce an insulin spike non-conducive to ketosis. For this reason a ketogenic diet should have no more than 20% of its calories coming from protein making a good starting point for most people a macronutrient breakdown of approximately 75% fats, 20% protein and 5% carbs (3:1); some highly insulin resistant individuals may need to bring down their protein level to 15% and their fats to 80% (4:1) to attain therapeutic levels of ketones (>2Mmol) (7). Historically this diet has been used therapeutically used since 1921 for the management of epileptic seizures with great success, as it provides an alternative fuel source for the brain in the case of glucose transporter (Glut) insufficiency and other issues not allowing glucose to pass the blood brain barrier; as ketones are independent of these mechanisms(10).

There are a considerable amount of studies exploring the use of ketogenic diets in cancer (mostly in animal models) looking for possiblemechanisms in which this dietary intervention could affect the outcome of aggressive cancers, whether life expectancy can be lengthened, quality of life improved or even remission attained. Since most still consider cancer a genetic disease instead of a metabolic disease some of these studies have examined how gene expression can be affected by eating a KD, as diet can affect genetic expression (epigenetics). One study analyzed a mouse model of glioma's (an aggressive form of brain cancer) reaction to a KD and compared the gene expression of 4 groups: (1) Standard Diet (SD), no cancer; (2) SD + cancer; (3) Ketogenic Diet (KD), no cancer; (4) KD + cancer; looking for changes in genes known to affect cancer growth (11). The gene expression profiling showed that rats with glioma on a KD reversed their gene expression to a pattern that more closely resembles the gene patterning of the rats without cancer, than the one of the cancer rats on the standard diet. Genes related to the production of reactive oxygen species(ROS) and oxidative stress were also down regulated on the glioma plus KD group, compared to the glioma SD group as well as lower signaling of growth factors known to augment tumor size and metastasis. Even though the rat's tumors did not go into remission the average survival period of the glioma plus KD went up to 25 days past tumor implantation comparedto 19 days for the SD group, a 32% increase in survival time. In a similar study, CT-2A (Malignant mouse astrocytoma) and a human malignant glioma (U87-MG) were implanted in mice and observed for 45 days, the mice were divided in 3 groups: a Standard Diet unrestricted (SD-UR), a Ketogenic Diet unrestricted (KD-UR) and a restricted Ketogenic diet (KD-R) (12). The mice in the (KD-R) had a 65% smaller mouse tumor and 35% smaller human glioma compared to the SD-UR group, as well as their survival time was almost doubled. When comparing both unrestricted groups the KD group had smaller tumor size and increased survival time, as well as lower blood glucose levels and higher b-hydroxybutyrate levels, however the biggest improvements were seen when calorie restriction and KD were combined, which is very common when following a strict KD. The study also looked at genes for ketone body metabolism on healthy brain cells compared to the malignant tumor, as these are severely downregulated it would make sense to utilize this genetic testing to measure how sensitive a cancer might be to this type of therapy.

At this stage, human research into this type of dietary intervention is still in the pilot trial stage to test for feasibility, adherence and possible side effects, before moving to larger sample sizes and longer interventions. In a pilot trial of 10 patients with advanced metastatic cancer investigators measured and compared: macro-nutrient intake, body weight, b-hydroxybutyrate, insulin, and insulin-like growth factors-1 and -2 and an FDG-PET scan at the beginning and end of a 4 week intervention with a ketogenic diet (13). Adherence to the diet was highly associated to the level of b-hydroxybutyrate measured at the end of the study and was compared to the level of the same individual at the beginning of the study. At the end of the study 4 of the 10 subjects had achieved a stable disease status plus one partial remission; it was observed that their levels of ketones were triple compared to those of the subjects whose disease was still progressing. Another worthy observation was that all participants spontaneously reduced their caloric intake by an average of 35% even though they were encouraged to increase their food consumption. This natural appetite suppression related to KD(14) may be an added bonus as some studies have proposed calorie reduction to prevent cancer, delay onset or as treatment(15). A small study of 5 patients with Tuberous Sclerosis Complex (TSC), which develop tumors along multiple organs (and between 80-90% also develop epilepsy),who were being treated with a KD for their drug resistant epilepsy was followed for 5 years to observe if the diet seemed to have a desirable effect on their tumor progression(16). The researchers hypothesized that the progression of their tumors might be slowed down since they were already adhering to a strict KD for seizure control and mTORC1 (mammalian target of rapamycin complex-1) pathway is reduced as well as thelevels of insulin are. Although 3 out of 5 patients' condition remained stable, tumor growth was observed in 2 of the 5 patients; new renal AML (renal angiomyolipomas) and a SGCTs (sub ependymal giant cell tumors) in the brain while on the KD diet. Another human pilot trial with 16 adult patients with advanced metastatic tumors (most were at end stage) and no clear conventional treatment options left, were instructed how to follow a KD (less than 70g carbs/day) for 90 days and they were given ingredients to make a lipid/protein shake for

convenience during the intervention (17). During the 3 months, every 2 weeks' blood was drawn, a Quality of Life questionnaire (ECOG-QLQ C30) filled out and a new nutrition packet was sent out. During the process of the intervention all but 5 dropped out for various reasons (2 died, others because of progression of the disease and others because they felt unable to follow the diet), the 5 that completed the intervention had a stable disease at the end and felt that an improved emotional state and less insomnia along as other positive aspects of life, but not without some of aspects worsening, as is to be expected because of their advanced stage of disease. No severe side effects were associated with the KD (temporary constipation and fatigue were the most common). Though the diet was well tolerated by 5 of 16 patients for 3 months and 7 for at least 5 weeks' adherence is feasible but challenging for most adults, as most find it hard to make such a drastic dietary change. Most blood parameters measured improved (blood glucose, cholesterol, LDL & LDL/HDL) as well as most perceptions of their quality of life. Among the limitations observed in this study is that 70g of carbohydrate is too high to produce ketosis in every patient, as lower levels are needed for more insulin insensitive individuals (this can be appreciated in table 4 where you can see that 4 out of the 10 evaluated for blood ketones did not even maintain the minimum required to be in mild ketosis, for half of the study). As it seems that no large human studies have been performed to ascertain the effects of a ketogenic diet in cancer treatment further studies with a larger sample and of longer duration are needed to be able to draw better conclusions.But if confirmed in larger studies, this type of dietary manipulation may be a viable non-toxic therapeutic option.

Malignant Gliomas (brain cancer) have a very high mortality rate and are very difficult to remove surgically since they do not have defined boundaries, the standard of care is partial removal of the tumor followed by chemotherapy, radiation or both. A study looked at an intracranial bioluminescent mouse model of malignant glioma and implementation of a KD based on the consumption of KetoCal (KC), a nutritionally complete 4:1 (fat: protein+carbs) ready to drink ketogenic formula(18). The mice were divided in 4 groups: acontrol group consisting of 19 mice fed their standard diet chow (SD), the KetoCal group (19), standard diet plus radiation (11) and 11 who received radiation plus Keto Cal. The KC only grouped survived 5 extra days compared to the SD group (28 vs. 23), the group that received radiation with a SD survived 41 days in average and the KC plus radiation group went into complete remission. The KC plus radiation group stayed on KC for 101 days after tumor implantation and afterwards were switched to their standard chow and observed for 200 extra days and no signs of gliomas were observed. This study seems to point that for very aggressive tumors such as gliomas it may not be advisable to forgo radiation as the radiation and SD group outlived the KD without radiation group, however the real value seems to be in combining a KD regimen with radiation to help their chances of survival, as all in this combined therapy group had no sign of gliomas, even 200 days after discontinuing the diet.

Tumors often exhibit abnormal vasculature which creates hypoxic (low oxygen) pockets which increase the glycolytic dependency of these cancers, promote faster proliferation and provide chemotherapy and radiation resistance. Hyperbaric Oxygen Therapy (HBO2T) uses 100% oxygen at higher than normal atmospheric pressures (>1At) this can saturatethese pockets with oxygen, diminishing their hypoxic effect(19). For this reason and their findings in previous studies (by these same researchers) utilizing the ketogenic diet in the treatment of Glioblastomas in a rat model they performed a study in which they divided their mice in 4 groups: A Standard Diet (SD) control, a SD plus HBO2T group, KD alone and KD combined with HBO2T. They compared their survival times and the SD mean survival time was 31 days, the SD + HBO2T= 39; KD alone = 49 and KD + HBO2T 55.5 days, showing a 56.7% and 77.9% increase in survival time for the KD only and KD + HBO2T group respectively. The increase in survival time also correlated with the lowest levels of blood glucose and highest ketone levels which were observed in the KD groups with the KD +HBO2T being the biggest change in both. These findings seem to point to the fact that the ketogenic diet can be a synergistic player when combined with other effective treatments against cancer. In addition, Intravenous Vitamin C may also be a synergistic cofactor in this suggested therapeutic protocol, since Vitamin C competes with glucose and its anticancer action is enhanced by oxygen (20).

Conclusion

Cancer is the second largest killer in the US and Puerto Rico as well as many developed countries but once the disease spreads the chances of survival are very small for which better treatment options are being actively searched. Per the data analyzed in this literature review, results in animal models utilizing the KD by itself brought increased survival time of 32%, to 77.9% and when combined with Hyperbaric Oxygen Therapy and radiation led to a complete remission. This seems to point to the usefulness of the diet by itself but even more so to the value of combining it with othernon-toxic treatments (HBOT, IV Vit C). Even though human trials have shown promise at this stage no large cancerstudies have been performed using the KD. We believe that future research will prove the effectiveness of this dietary manipulation in the treatment of human cancers.

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