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A NUTRITIONAL PERSPECTIVE OF KETOGENIC DIET IN CANCER

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Abstract

Thanks to capacity of modification of cellular metabolism, acting on blood glucose levels and, consequently, on many genetics, biochemical and enzymatic mechanisms, the ketogenic diet **(KD)** is used as a promising and good adjuvant therapy on treatment of many types of cancer.

A big number of preclinical (mostly) and clinical trials have been programmed and successfully done with good results. Nowadays, researchers want to continue to develop better ketogenic protocols to improve the effects on treatment of cancer, besides classic chemo- and radiotherapy, putting attention on composition of diet, ratio between fats and carbohydrates and optimal time point during therapy and the stage of disease.

Keywords: *Ketogenic diet, cancer, adjuvant cancer therapy.*

Introduction

This review wants to describe rational bases of use of ketogenic diet (KD) on treatment of oncological disease. Modifications on hormones, cellular pathways, genes expressions are the result of the lowering of the glucose levels on the blood due to a strong reduction of carbohydrates of the diet, typical characteristic of KD.

Is often observed that this condition brings to improve the efficacy of chemo- and radiotherapies against cancer cells.

Finally this work will make mention of a recent review edited on "Molecular Metabolism" journal about most of studies (in vitro, preclinical and clinical) done from 1979 till 2019 on a great number of different types of cancer treated with KD and conventional cancer therapies, demonstrating a global good effect that leads to further developments.

Methods

This review is based on the existing knowledge on the topic based on published research published on scientific journals (PubMed).

Discussion

Nowadays surgery, chemo and radio therapies are the standard instruments used on treatment of cancer disease. Therefore, there is a great attention on a particular dietetic regimen and a ketogenic diet, as an adjuvant anticancer therapy appears to sensitize most types of cancer to standard treatments.

The ketogenic diet is a hi-fat, low carbohydrates, adequate amounts protein diet that leads to lowering the blood glucose levels and, at the same time, increasing of ketone bodies, as result of an augmented lipolysis and beta-oxidation of fatty acids. It was observed that cancer cells, depending their energetic metabolism mostly on cytoplasmatic glycolysis (Warburg effect), are strongly conditioned on growth (1).

Instead, normal cells take advantage from utilization of ketone bodies as alternative energy source, using them on tricarboxylic acid cycle (Krebs cycle) and mitochondrial oxidative phosphorylation. Actually, it was observed that in many types of cancer cells there are many mutations on mitochondrial DNA, alterations on electron transport chain system (ETC) with consequent disfunction of oxidative phosphorylation (2). These facts can explain why some cancer cells have a difficult adaptation to low levels of glucose and high levels of alternative source of energy (ketone bodies) that cannot utilize via mitochondrial oxidation.

Low levels of glucose, guaranteed by a KD, can sensitize cancer cells to therapies inducing an inhibition of pentose phosphate pathway, fed by availability of glucose inside the cancer cells. This pathway, in normally condition, thanks to elevated glycolysis linked to availability of glucose, can provide reducing equivalents (NADPH) that can compensate the big amount of species of reactive oxygen (ROS). The level of oxidative stress in cancer cell, during a KD, can be bigger because of the lack of NADPH during a KD. This can explain why some kind of tumor, like in lung and pancreatic cancer - bearing mice, can be reduced with a combination of KD and radiotherapy (3).

Hormonal mechanism are involved too. The reduction of blood levels of insulin and IGF-1, due to lowering of blood glucose linked to low levels of carbohydrates of the diet, seems to be important in the effect of KD in many studies. These two hormones are linked to tumorigenesis via PIK3 pathways. Phosphoinositide 3-kinases (activated by insuline) play an important role in progression and growth of cancer cells when there are mutations on correspondent genes. Today many potent anticancer drugs are PIK3 inhibitors and their activity is enhanced by low levels of insulin (4).

Ketone bodies (aceto-acetic acid and beta-hydroxybutyrate) are augmented during ketosis inducted by Ketogenic diet and their action is overall anticancer and anti-inflammatory, even if in some case of preclinical studies the effect seemed to be opposite. Particularly, beta-hydroxybutyrate (BHB) showed an inhibition of histone deacetylases (HDACs) that are involved in mechanism of genes

expressions. In many types of cancer it was observed an excessive activity of these enzymes (5).

A link with HDACs activity, inhibited by BHB are the high levels of oncosuppressor P53 acetylated that is more expressed during a Ketogenic Diet (6).

BHB has an anti-inflammatory action, shared with analog molecule butyric acid that can be provided by fermentation operated by gut microbiota. These effects consist principally in reduction of pro-inflammatory cytokines like IL-1, IL-6, Il-8, TNF-alfa, vascular endothelial growth factors (VEGFs), NLPR3 inflammasome (7-9).

However, ketone bodies were associated to a progression and growth of some kind of tumor, leading to a paradox on the action of beta-hydroyibutyrate.

This paradox can depend, as suggested by Rodrigues et al., on phenotypical energetic characteristics of cells. "Oxidative" cancer cell could be able to consume ketone bodies instead of "glycolytic" cancer cell that can survive only with a good and appropriate amount of glucose utilized via cytoplasmatic glycolysis (10).

Similar unexpected effects were found in breast cancer (in vitro and in breast cancer in mice) and melanoma studies, where researchers understood that ketone bodies can be an important signaling molecules that can enhance progression of cancer (11-13).

It is clear that, even if a lot of studies have been done, there is necessity to understand other numerous mechanisms that are involved in all aspects of cancer.

In a review posted on 'Molecular Metabolism' journal (June, 2019) authors collected an enormous quantity of data related to the relationship between Ketogenic Diet and cancer (14).

Data are related to studies done from 1979 to 2019.

Studies collected are in vitro studies, preclinical and clinical trials and the goal of the entire review was to highlight major findings emerged.

Principally, the results are positive effects of the KD as adjuvant therapy showing slowed tumor growth, promoting survival, block of cancer-induced cachexia.

In a partial, little rate of cases (10% cases counted by authors in the total cases taken in exam) some studies highlighted unfavorable effect due to particularity of cancer, for example the case of BRAFV V600E mutated melanoma, where ketone body acid acetoacetic promoted proliferation (15).

This, like other cases, must induce scientific community and researchers to study the effect of KD in every specific type of tumor, like authors say. Alteration on genes and particular phenotypical characteristics of cancer can be the reasons of why ketogenic diet, sometimes, couldn't work.

Clinical studies are still few. Mostly are case-reports and pilot studies, but it doesn't exist randomized controlled trials with a large number of patients.

The principal results in clinical studies are reported on 'table 2' of the mentioned review.

The positive facts, that surely emerged and are common in all studied cases, are the improvement of quality of life (QoL), of overall health status, reduction of fat mass and preserving of lean mass. Furthermore, a global improvement of metabolic parameters (lipid profile, insulin and glucose levels).

It is finally observed that it is very import for patient to be sustained in adherence to diet, providing an appropriate supplementation with vitamins and minerals to avoid the possibility of lack or deficiency of these micronutrients that could bring to some collateral effects (headache, gastrointestinal disorders, weakness).

Generally, the ketogenic diet is safe and good tolerated. None of the studies reported any serious adverse events or toxicity related to the KD.

Conclusion

Today ketogenic diet seems to be a valid adjuvant dietetic therapy on treating of different kind of tumors. Many trials, preclinical (mostly) and clinical,

highlighted good results and give a cheering prospective for the future.

As the good and positive results are more numerous than adverse effects, researchers are

engaging, more than in the past, to improve the effect of KD on treating of oncological disease.

New studies focus on refine better ketogenic protocols for matching better with peculiarity of different cancers. It's important to define the optimal time point (before, during or after the therapy) and even the best composition of diet itself (ratio of fat/carbohydrates, amount of protein and quantity of calories).

The goal is to maintain good tolerance and safety of KD but, above all, to show the effectiveness of KD as an adjuvant strategy on cancer treatment beside standard therapies.

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