Potential Value of Positron Emission Tomography (PET) in Evaluating the Ketogenic Diet as Anticancer Therapy

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Abstract: Positron Emission Tomography (PET) imaging is a noninvasive and extraordinarily sensitive imaging modality that provides a functional and metabolic assessment of normal or diseased tissue. [18F]-fluorodeoxyglucose PET imaging (FDG PET) is widely used clinically for tumor imaging, and has been proven to improve the diagnosis and subsequent treatment of cancer patients. The rationale behind FDG PET imaging is the Warburg effect, which states that there is increased glycolysis in cancer cells, even in the presence of oxygen, making it possible to detect cells exhibiting increased glycolysis, thus diagnosing even small tumors. The ketogenic diet (KD) with low carbohydrate and high fat intake has been used as an alternative treatment for cancer and other diseases, with nearly a century of use for reducing seizure onset in epileptics. The cellular mechanism underlying KD therapy is also based on the Warburg effect. The increased ketolysis stimulated by KD therapy inhibits the abnormally elevated glycolysis in cancer cells, leading to reduced tumor growth and metastasis. In this review, we first describe the Warburg effect as the common biological basis connecting PET and KD therapy. This paper also provides overviews of PET imaging and KD therapy. Two newly published papers, one regarding the molecular mechanism of KD therapy in the treatment of cancers, another on the *in vivo* PET imaging of cerebral metabolism of glucose and ketone bodes in humans after a moderate KD, are thoroughly reviewed. Furthermore, this review describes how PET imaging may be applied to study the effects of KD therapy in humans and animals, and which currently available PET tracers can be used to image glucose and ketone metabolic pathways.

Key Words: PET imaging; Warburg effect; Ketone bodies; Fatty acid; Cancer

Introduction

There are more than 8 million cancer-related deaths per year around the world [1]. Surgery, chemotherapy and radiotherapy are the most common treatments for patients with cancer. However, all of these traditional therapeutic methods are limited by a lack of efficacy, contraindications, and side effects. Although a number of new therapeutic methods have been introduced during the past few decades, such as immunotherapy, targeted therapy, hormone therapy and stem cell therapy, the patient outcomes remain poor for many types of cancer.

The ketogenic diet (KD), originally developed for the treatment of epilepsy, and has been reported as a novel anticancer therapy that leads to significant clinical improvements for a variety of cancers, such as glioblastoma multiforme [2]. The KD is a high-fat, very-low-carbohydrate, adequate protein diet that simulates a fasting metabolic state by decreasing the glucose level while simultaneously increasing the levels of ketone bodies in the blood. The KD has been used for the treatment of epilepsy for more than 90 years in the United States and many other countries. A wide range of clinical data has published on the efficacy of KD in treatment of children with pharmacoresistant epilepsy [3]. Several clinical studies have also shown that the KD is valuable for patients with a variety of cancers, leading to reductions in tumor volume and tumor growth rates, improvement of the patient quality of life, prolongation of survival, and enhancement of sensitivity to radiotherapy and chemotherapy [4,5] in patients with different types of tumors, including brain tumors [6], colorectal cancer [7], breast cancer [8], lung cancer [9] and glioblastoma [10,11]. However, most of these data were contained in clinical case reports, and large-scale clinical trials are still lacking.

The abnormal increase in glycolysis present in cancer cells, known as the Warburg effect is a pathological basis for using the KD in cancer patients. Positron emission tomography (PET) imaging uses a radioisotope-labeled molecule as a tracer to investigate physiological or pathological changes *in vivo*. One widely used trace for PET imaging is [18]F-fluorodeoxyglucose (FDG). FDG can identify areas of high glucose uptake or metabolism in the body. FDG is transported into cells by glucose transporters and is phosphorylated by hexokinase to 18F-FDG-6-phosphate. At this step, FDG cannot be further metabolized through the glycolytic pathway, and FDG metabolites are trapped inside of cells due to their highly polar nature [12]. The Warburg effect states that cancer cells utilize much more glucose than normal cells [13]. This is a

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rationale for using FDG PET to image tumors in clinical practice [14]. Thus, FDG uptake is a good biomarker of malignant tissue. When FDG is injected into the bloodstream, the uptake of FDG in cancer tissues is significantly higher than in healthy tissues, and this increased accumulation of FDG can be observed 40-60 minutes after injection.

The Warburg effect, as an essential hallmark of cancer cells, is the common biological basis for both KD therapy and PET imaging. For this reason, PET imaging can play an important role in studying the effects of KD therapy on cancer, and for evaluating its therapeutic efficiency in the treatment of cancer patients. Currently, very few reports can be found in literature regarding the application of PET imaging related to KD therapy for cancer.

The aim of this review is to provide a summary of the current knowledge on: 1) the Warburg effect and its role in cancer metabolism; 2) the impact of KD therapy on metabolic disorders, including cancer and neurological diseases; 3) the roles of PET imaging in oncology; and 4) the potential value of PET imaging in research on KD therapy.

Two significant papers were recently published on the changes in gene expression related to KD therapy and on using PET imaging to follow ketone body metabolism in humans. These papers will also be carefully reviewed.

The Warburg Effect

Glucose is a major source of energy for living organisms. There are two different pathways involved in the metabolism of glucose: anaerobic and aerobic. The first process of glucose metabolism converts one molecule of glucose into two molecules of pyruvate, with the concurrent generation of two molecules of adenosine triphosphate (ATP). This process occurs in the cytoplasm, and is called glycolysis. Since oxygen is not required for this process, it also is referred to as anaerobic glycolysis. Pyruvate is an end product of glycolysis. As a metabolic intermediate with several potential fates, pyruvate enters into the mitochondria, where it participates in the tricarboxylic acid cycle. (Krebs cycle) and oxidative phosphorylation to generate additional ATP Via this pathway, 36 molecules of ATP are generated from one glucose molecule. This process is called the aerobic process or aerobic respiration since it requires oxygen. Therefore, in normal cells, the majority of the cell's energy is generated from mitochondrial oxidative phosphorylation.

During the 1920s, German scientist Otto Warburg studied the fermentation of glucose in mammalian tissues. Warburg and his colleagues found a significantly increased conversion of glucose to lactate in cancer cells compared with normal cells. Glucose was found to be fermented even in the presence of normal levels of oxygen in cancer tissues, a phenomenon termed aerobic glycolysis [13]. Warburg hypothesized that, by utilizing this process, cancer cells can produce a relatively high amount of energy, regardless of the availability of oxygen. Although lactate fermentation allows them to grow under hypoxic conditions, cancer cells generate ATP less efficiently than normal cells that metabolize glucose through oxidative phosphorylation in the mitochondria. Thus, a high uptake of glucose is required to meet the energy needs for rapid tumor progression. This is the rationale underlying the use of PET imaging in detecting tumors in clinical practice [12].

Abnormally increased glycolysis is a characteristic of cancer cells. In the earlier years after the Warburg effect was found, it was hypothesized that cancer cells had mitochondrial dysfunction. However, increasing evidence has shown that the mitochondria are active and functional in cancer cells [15]. In fact, cancer cells show complex, dynamic behavior that allows them to survive even under the most unfavorable conditions of substrate and oxygen stress. In recent years, studies of the Warburg effect have increased extensively, with more than 20,000 annual publications on the topic. This extensive research on the Warburg effect and its functions in cancer cells have advanced our understanding on tumor metabolism, and therapeutic and imaging targets. In the following sections, the functions of the Warburg effect have been considered based on experimental data.

Rapid ATP Synthesis

Considering the efficiency of energy supply in cells, aerobic glycolysis is a poorer means of generating ATP compared with the amount of ATP obtained from mitochondrial oxidative phosphorylation. The net number of ATP generated through aerobic glycolysis is only two from each glucose molecule. In comparison, mitochondrial respiration generates 36 ATP from one glucose molecule. However, the rate of glucose metabolism through aerobic glycolysis is 10-100 times faster than the complete oxidation of glucose in the mitochondria. Therefore, cancer cells are able to generate more ATP in a shorter period, independent of the oxygen content in the microenvironment. However, much more glucose is required to achieve this energy production to meet the requirements for the rapid growth of tumor tissues [16].

Materials Used in Biosynthesis for Tumor Development

Another proposed reason for the abnormally increased level of glycolysis in cancer cells is to provide biological materials for rapid tumor growth. It is

considered that the increased glucose consumption used in aerobic glycolysis provide a carbon source for anabolic processes related to cancer cell proliferation. These carbon molecules are diverted into multiple branching pathways. Then they become the essential biosynthetic materials for generating nucleotides, lipids and proteins [17].

Microenvironment for Cancer Proliferation

An acidic microenvironment is beneficial to cancer cells. This is particularly true with regard to invasion, because those hydrogen ions can diffuse into the surrounding environment and alter the tumor-stroma interface. During the process of aerobic glycolysis, glucose molecules are metabolized into pyruvate to yield two net ATP. Pyruvate is then converted to lactate in the cell cytoplasm, leading to acidosis. This has been shown in several investigations, such as in a study of tissue-associated macrophage polarization [18,19].

Cell Signaling and Homeostasis of Reactive Oxygen Species

Recent studies have shown that the mitochondrial redox potential can be directly or indirectly altered by increased glycolysis, ultimately leading to changes in the generation of reactive oxygen species (ROS) [20,21]. Maintaining the homeostasis of ROS is an essential requirement for all living organisms, including normal and malignant cells. Excessive ROS can cause tissues damage, including damage to the cell membrane, nucleic acids, proteins and enzymes. In contrast, insufficient ROS disturbs cellular signaling processes, such as cell proliferation and the inactivation of phosphatases.

The Ketogenic Diet

The rationale for using the KD as a therapy for a variety of diseases, including epilepsy, motor disorders and even cancer [22], is also based on the Warburg effect. Since tumor tissues use glycolysis to provide energy and biomolecule, they require large amounts of glucose to meet the needs for rapid growth. As a result, the shift of metabolism in cancer cells towards increased glycolysis and away from the Krebs cycle and oxidative phosphorylation in the mitochondria occurs even in the early phase of tumorigenesis. This allows tumor tissues to undergo rapid proliferation even in the presence of dysfunctional mitochondria. Based on this increased need for glucose resulting from metabolic dysregulation, it has been postulated that a reduction in tumor growth could be achieved by reducing glucose availability through the KD, or another diet with a high-fat and low-carbohydrate composition.

In subjects on the KD, the increased blood ketones become the main energy supply for normal tissues. Both preclinical work and clinical studies from a number of laboratories and hospitals have shown that the KD is benefit for a variety of diseases. As reported by Klement RJ [23] in a meta-analysis, the KD significantly prolonged survival in experimental cancer models in mice, even when used as a monotherapy. In humans, KD therapy has been shown to be benefit for many cancer patients, such as those with pancreatic, lung, head and neck, and breast cancer, as well as glioblastoma [4].

There are four main categories of KD that are generally followed: 1) the long chain triglyceride-based diet consists of a classical ratio of fat to nonfat (protein and carbohydrate) of 4:1, 3:1, 2:1, or 1:1. 2) The medium chain triglyceride-based diet is not based on diet ratios, but has a percentage of calories from caprylic and capric acids to create ketones. 3) The modified Atkins diet is specifically used to treat epilepsy with a less restrictive and more palatable dietary treatment. 4) The low glycemic index treatment includes a more moderate intake of carbohydrates with a target glycemic index lower than 50. In the clinical practice, the choice of these diets must be based on the clinical diagnosis, age, gender, weight, activity level, and the expected compliance [4].

A recent report examined the expression of two key enzymes involved in regulating the ketolytic pathway, 3-hydroxybutyrate dehydrogenase 1 (BDH1) and 3-oxoacid CoA transferase 1 (OXCT1), and demonstrated that tumors with low expression of ketolytic enzymes cannot metabolize ketone bodies, leading to a better response to KD therapy [24]. At the molecular level, this study provides evidence that KD therapy affects the cellular glycolytic and ketolytic metabolic pathways *in vitro* and *in vivo*. This study will be discussed in greater depth later in this paper.

PET Imaging

The broad and robust diagnostic utility of imaging radiopharmaceutical fluorine-18 FDG has been largely responsible for the clinical success of PET in applications for cancer patients. In oncology, FDG PET imaging is used to diagnose, stage, and assess the response to treatment of various cancers.

Sensitivity is an important parameter for evaluating clinical imaging modalities with the ability to detect a particular diseased lesion. In a general sense, anatomic imaging modalities, such as MRI and CT, are usually more sensitive than nuclear imaging or PET imaging. However, this assumption is correct if only considering a subcentimeter nodule or a larger lesion without uptake of a nuclear tracer. In the context of nuclear and molecular imaging approaches, sensitivity refers to the ability to detect a diseased lesion at molecular level, rather than in the sense of the lesion's physical size or

volume. In this regard, PET imaging is a versatile modality that can diagnose and characterize tumors based on molecular characteristics, and with high sensitivity. PET is an order of magnitude more sensitive for detecting the presence of malignant cells than other medical modalities, such as CT and MRI, because it can detect radiolabeled agents in the picomolar concentration range.

As mentioned above, FDG is a widely used PET tracer for imaging glucose metabolism. To study the impact of KD therapy, PET tracers for imaging pathways related to fatty acid metabolism are required. There are already several imaging tracers for fatty acids that are available and can be used for PET.

[18F]-FTHA

To image long-chain free fatty acids in cells, [18F]-fluoro-6-thia-heptadecanoic acid (FTHA) was developed. As a fatty acid analog, FTHA enters cells by the same mechanism as natural fatty acids and undergoes partial metabolism before being trapped in the mitochondria. Thus, the tissue accumulation of FTHA represents total fatty utilization, including both storage and beta-oxidation.

[11C]-acetate

In living tissue, [11C]-acetate is quickly metabolized into acetyl-CoA, which can either enter the Krebs cycle in the mitochondria, or be taken up and used as a structural lipid [25]. Washout of this tracer after injection is related to oxygen consumption, and uptake at later time points represents the rate of fatty acid synthesis. It is a particularly promising PET tracer for detecting renal, pancreatic and prostate tumors. Additionally, this tracer can also be used for studying myocardial oxidative metabolism and regional myocardial perfusion [26].

[11C]-palmitate

This tracer is also well-established for targeting fatty acid metabolism and is an optimal choice with respect to its binding affinity, because it does not need to be coupled with a bulky chelator molecular for imaging proposes. It behaves like any other natural non-synthesized fatty acid, justifying why it is used as a gold standard when studying modified molecules. However, [11C]-palmitate has a half-life of only 20 min, making it necessary to have an in-house cyclotron, significantly restricting its use.

[11C]-acetoacetate

Under normal conditions, glucose is converted to acetate to feed into the tricarboxylic acid cycle for energy generation. However, when the carbohydrate intake is low or during fasting, ketone bodies, mainly acetoacetate and hydroxybutyrate, are produced by the liver. Ketone bodies cannot be utilized in liver cells since they lack acetoacetyl-CoA transferase. Therefore, this tracer can be used to measure ketone body utilization by tumors and the brain.

Two Newly-published Papers Describing the Mechanisms by which the KD Exerts Anti-cancer Effects

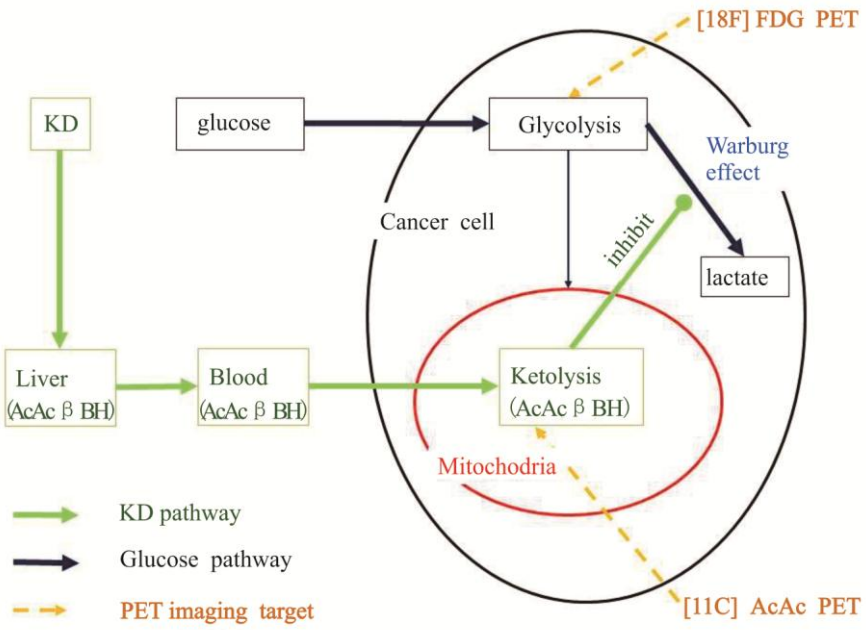

Figure 1 The overlap between the glycolytic pathways and the KD, and the sites targeted by PET imaging KD: ketogenic diet; AcAc: acetoacetate; βBH: β-hydroxybutyrate

There are two papers that were recently published regarding the metabolic changes that occur after beginning the KD. One focused on the changes that occur at the cellular level *in vitro* and in animal models, and the other examined the *in vivo* effects in humans using PET.

In the first study [24], the authors directly investigated the relationship between the gene expression of ketolytic enzymes and the response of malignant cells to KD therapy *in vitro* and *in vivo*. In this study, the authors focused on the gene expression of two key enzymes involved in the ketolysis of ketone bodies: 3-hydroxybutyrate dehydrogenase (BDH1) and succinyl-CaA:3-oxoacid CoA transferase (OXCT1). After screening 33 human cancer cell lines, two lines were selected for subsequent *in vivo* studies; HeLa with high expression, and PANC-1 with low expression. In nude mouse xenograft models derived from these two cell lines, an inverse relationship was observed between the expression levels of these ketolytic enzymes and the response to KD therapy. The xenograft tumors with low expression of BDH1 and OXCT1 were more responsive to KD therapy. The authors [24] hypothesized that tumor cells with low expression of ketolytic enzymes possess a weaker ability to metabolize ketone bodies to generate energy, leading to cancer cell death at last.

In the other study [27], the metabolic activities of glycolysis and ketolysis were quantified before and after KD therapy by PET imaging healthy human brains with [11C] acetoacetate for ketolytic metabolism and [18F]-FDG for glucose metabolism. An inverse relationship was found between brain glucose and ketone metabolism in health subjects with moderate shorterm ketosis induced by a very high fat KD (4.5:1; lipid:protein plus carbohydrates). The authors of that study found that the cerebral metabolic rate of acetoacetate significantly increased, and glucose decreased after subjects switched to the KD. This was the first study of the impact of the KD in humans using PET, the first report to quantify the metabolic changes in ketone bodies and glucose in the human brain after the introduction of the KD, and the first to report the quantitative changes in the cerebral metabolic rate of glucose across the brain-blood barrier (BBB). This study confirms that in humans undergoing short-term ketosis induced by a KD, the brain's overall metabolic rate is driven by the blood ketone concentration. It also demonstrated that the rate of glucose metabolism declines proportionally so as to meet, but not exceed, the brain's net metabolic needs. This PET protocol provides an opportunity to assess whether similar ketogenic conditions induce the same metabolic changes in cancer patients.

These two studies provide strong experimental evidence that KD therapy alters the intracellular metabolic pathways. These two studies are important because they provide mechanistic evidence to support the use of KD therapy in cancer patients. For many years, the rationale for using KD therapy was hypothesized to be due to the Warburg effect, although there were a few studies that showed conflicting findings [14]. These two recent studies provide clearer evidence of the effects of the KD on malignant cells, and suggest that PET can be used to monitor the impact of the KD in patients.

Suggestions for Using PET Imaging in Future Investigations of the Mechanism of Action and Application of KD Therapy

So far, there have been no studies on the application of *in vivo* PET imaging to assess the effects of KD therapy on cancer. As noted above, PET imaging can be used to assess both the cellular mechanisms of action and the effects of the KD. Thus, PET imaging will provide a powerful tool for further investigation of the mechanisms of action of the KD at the molecular level. Furthermore, PET imaging can also be used to evaluate the efficiency of KD therapy in studies in experimental animals, and eventually human clinical trials.

With regard to the choice of PET tracer(s), only one ketone pathway-specific probe, [11C] acetoacetate, has been used so far. Although this tracer provides precise information on the direct metabolic activity of ketone bodies, the use of PET tracers for other steps of fatty acid metabolism would also be valuable for investigating KD therapy, such as [18F]-FHTA, [11C]-Palmitate and [11C]-acetate, since the KD should affect all fatty acid metabolic pathways, rather than only those related to ketone bodies.

Conclusions

Increased cellular glycolysis has been considered a hallmark of cancer cells. Although the clinical relevance of this phenomenon (the Warburg effect) has been debated, more and more case reports and clinical studies have suggested that the phenomenon does occur and represents a potential target for diagnosing and treatment malignancy. The present review shows that KD therapy has led to significant clinical improvements in patients with a variety of diseases, including epilepsy and various cancers. Furthermore, the expression of genes involved in the metabolism of ketone bodies was demonstrated to determine the efficacy of KD therapy in animal models of cancer. In human studies using PET imaging, clear metabolic changes were noted in glucose and ketone body metabolism in the brain after patients had been on moderate KD therapy. Suggestions in exploring the impact of KD therapy using *in vivo* PET imaging are given.

Conflict of Interest

The author declares no conflict of interests.

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