

# Carbohydrate restriction in patients with advanced cancer: a protocol to assess safety and feasibility with an accompanying hypothesis

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Dietary carbohydrate restriction provokes systemic metabolic and cell signaling effects including down-regulation of insulin, insulin-like growth factors, fatty acid synthase, and other enzymatic and signaling targets. These effects as well as increased availability of fatty acids and ketone bodies may plausibly inhibit aggressive glycolytic cancers. We have designed a 28-day clinical trial diet of very low carbohydrate intake under nutritionist guidance to test the safety and feasibility in patients with advanced glucose-dependent solid cancers, determined by a positive baseline positron emission tomography (PET) scan using 18-fluorodeoxyglucose to demonstrate glucose avidity. Changes in a follow-up PET scan at study's end permit a surrogate measure of efficacy.

**I**n the 1920s, Otto Warburg described reliance on glucose fermentation as a unifying feature of cancer metabolism.<sup>1</sup> Although not universally applicable, the idea continues to be useful, especially in describing aggressive malignancies. Many cancers unable to derive energy from respiration are

restricted to the anaerobic glycolytic pathway. Increased glucose use relative to normal tissues is seen in these tumors. This observation is the basis of modern diagnostic imaging with F-18 fluorodeoxyglucose (FDG) positron emission tomography (PET) scans in detection, staging, prognosis, and therapy assessment of many malignancies, including those of the breasts, colorectum, lungs, cervix, endometrium, and ovaries.<sup>2</sup>

The possibility of using dietary carbohydrate restriction therapeutically to allow the host to compete against the tumor has been raised by several investigators,<sup>3-5</sup> but the idea requires scrutiny. Plasma glucose concentration falls only mildly, remaining in the normal range in normal-weight individuals<sup>6</sup> and in those trying to lose weight<sup>7</sup> using low-car-

## KEY POINTS

In a low-carbohydrate diet, the increased availability of fatty acids and ketone bodies may inhibit aggressive glycolytic cancers.

Studies have reported reduced tumor growth in animals whose dietary carbohydrate has been replaced with fat.

The authors are recruiting for a safety and feasibility clinical study using dietary carbohydrate restriction.

Eligible patients are those with advanced glucose-dependent solid cancers that are PET-avid.

The authors give details on the hypothesis and protocol for the study as well as contact information for referral.

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bohydrate diets. Simple tumor glucose starvation is therefore unlikely in humans.

Strict carbohydrate limitation, however, leads to distinct changes in signaling pathways and downstream metabolism, including moderate ketosis, fatty acid synthase inhibition, reduced secretion of insulin,<sup>8</sup> insulin-like growth factors, and several inflammatory cytokines. Studies report reduced tumor growth in animals made ketotic by replacing dietary carbohydrate with fat,<sup>9,10</sup> an effect also described in tumor cell cultures incubated with ketone bodies.<sup>11,12</sup> Fatty acid synthase inhibition has been associated with increased apoptosis of breast carcinoma cells.<sup>13</sup> The effect of ketone bodies themselves or other features of the ketotic environment, uncoupling proteins or relief from high levels of hormonal stimulation, may be more important than competition for substrates.

Similar reports in humans are limited. Safety of a 1-week very low carbohydrate ketogenic (VLCK) diet was demonstrated by Fearon et al in five subjects with cancer.<sup>14</sup> A case study by Nebeling et al reported on two children with malignant astrocytoma, both of whom demonstrated 22% reduced FDG uptake on PET scans, accompanied by clinical improvement after 8 weeks of a ketogenic diet.<sup>3</sup> Carbohydrate restriction in humans has been hypothesized to have potential benefit for prostate<sup>4</sup> and brain<sup>5</sup> cancers as well as for prevention of other cancers.<sup>15</sup>

We have designed a 1-month safety and feasibility study of a VLCK diet in subjects with advanced FDG-avid solid tumors, using PET scanning as a surrogate measure of efficacy. Short- and intermediate-term studies have shown carbohydrate restriction to be safe in individuals not only for weight loss but for reduction of cardiac risk factors during weight maintenance.<sup>6,16</sup> In this article, we describe the clinical trial design and

provide a synopsis of the motivating hypothesis for exploring VLCK diets in cancer.

## Objectives, materials, and methods

### Study aims

The primary study objective was to determine the safety and feasibility of a VLCK diet in a 28-day trial in subjects with advanced, solid, FDG-avid cancers. The secondary study objective was to compare changes in an FDG-PET scan from study initiation to trial termination as a surrogate measure of efficacy.

### Patient selection

Patients are referred by the Department of Medicine's Oncology Division at Montefiore Medical Center or are solicited through Independent Review Board (IRB)-approved advertisement. Patients also may locate our study at ClinicalTrials.gov (trial id: NCT00444054), Emerging-Med.com, or at our website (<http://www.aecom.yu.edu/RechargeTrial/>) directly or via search engines.

### Eligibility criteria

Subjects must have solid, metastatic, FDG-PET-avid tumors. Patients have either failed to respond to or refused chemotherapy or are on a "chemo holiday" and are not concurrently receiving chemotherapy or radiation therapy. Patients with tumors unlikely to be PET-avid (eg, prostate cancer) are not considered eligible.

Exclusions include a body mass index < 22 lb/in<sup>2</sup>; renal or renal stone disease; and concurrent medical or other conditions that would make adhering to a VLCK diet difficult.

### Interventions

Patients test their compliance in a 2- to 3-day trial of a VLCK diet (< 20 g/d) under the guidance of a nutritionist. If the diet is tolerated,

a baseline PET/CT scan is obtained (Phillips, Inc) to determine FDG avidity. If the scan is positive for uptake in primary or metastatic sites, the VLCK diet is then administered for up to 28 days. Patients receive a digital scale for daily home weight measurements and are supervised with frequent phone calls; weekly office visits (including office weight measurement); and blood sampling for serum electrolytes, glucose, creatinine, and plasma beta-hydroxybutyrate (BHB) concentration to determine metabolic effects and assess compliance. A weekly nutritionist's review of written food records permits reconstruction of calorie, protein, carbohydrate, and fat content (FoodWorks software, Version 8.00. Long Valley, NJ: The Nutrition Company; 2000).

All obvious sources of sugar and starch are eliminated, including bread, pasta, rice, potato, sugary drinks, and desserts. Fruit and vegetable portion sizes are limited in accordance with our ketogenic goal. High protein foods, including beef, pork, poultry, fish, eggs, many cheeses, and unsaturated oils for cooking, are encouraged along with a variety of green vegetables. Supplementary low carbohydrate shakes are provided (1–2 g of carbohydrate and approximately 170 calories).

We are mindful that excessive weight loss would be undesirable in patients with cancer. Therefore, weight loss of > 5% baseline body weight triggers immediate scrutiny for possible study discontinuation. An exit PET/CT scan is obtained if patients have participated in the trial for 14 days.

### Rationale for 1-month study duration

Several factors should be considered when assessing the duration and design of a VLCK diet. Ketosis is desirable, both to aid assessment of compliance and to maximize effects that may favor normal tissues compared with more metabolically lim-

ited cancers (see Study rationale and hypothesis). The human and animal studies cited were successful at inducing ketosis within 7 days. The induction phase of an Atkins diet also has been shown to induce ketosis (10 to 20 fold elevation of BHB) in less than 1 week.<sup>17</sup> A human study<sup>3</sup> assessed tumor response at 8 weeks, whereas animal studies<sup>9,10,18</sup> showed responses in less than 4 weeks. Therefore, it is methodologically feasible in a potentially fragile patient population to attempt a 4-week dietary trial.

Further, it is not implausible to detect a selective metabolic effect on the cancer using PET scans. Reports demonstrate FDG-PET's ability to detect early efficacy of cancer therapy.<sup>19</sup> In lung,<sup>20</sup> breast,<sup>21</sup> colorectal,<sup>22</sup> and other cancers, the efficacy of a single cycle of chemotherapy may be assessed by the FDG-PET response of lesion uptake. In lymphoma, PET scans have been used successfully, even during treatment<sup>23,24</sup>; one study showed a 60% decrease in FDG uptake within 7 days of initiation of chemotherapy.<sup>25</sup>

#### *Criteria for achievement of study aims*

If individual patients cannot complete 4 weeks of the VLCK dietary intervention, because 14 days are adequate to have provoked ketosis, completion of at least 2 trial weeks permits evaluation of both study aims.

- Safety and feasibility are determined by finishing at least 2 study weeks without trial termination from intervention-related adverse effects.
- Efficacy is measured by a surrogate marker, a change in FDG-PET uptake of cancer lesions between baseline and exit PET scan. Standardized uptake values (SUVs), which represent a percent uptake of the injected radioactive dose normalized to body mass, are used.<sup>26</sup> Changes in SUV representing progressive disease, stable disease, and partial remission are those established by the European Organization of Radiation Therapy criteria.<sup>26</sup>

## **Study rationale and hypothesis**

### *VLCK diets, starvation, and plausible mechanisms of cancer inhibition*

Metabolic similarities of starvation and carbohydrate restriction have long been observed.<sup>27,28</sup> In mouse models of breast cancer, fasting (both acute<sup>29</sup> and intermittent<sup>30</sup>) has been shown to improve survival and reduce tumor size. Similarly, a mouse brain tumor model<sup>31</sup> demonstrated improvement during treatment by caloric restriction. In humans, weight loss was shown to improve lymphedema in human breast cancer.<sup>32</sup>

Well-described metabolic effects of starvation and carbohydrate restriction include many that may plausibly inhibit cancer growth, either individually or in concert. They include ketosis; fatty acid synthase inhibition; fatty acidemia; and reduced secretion of insulin, insulin-like growth factors, and inflammatory cytokines.

- Ketosis: In normal tissues with mitochondria, ketone bodies supply acetyl coenzyme A (CoA) for the TCA (tricarboxylic acid) cycle.<sup>33</sup> At higher levels, glycolysis may be repressed by feedback inhibition of phosphofruktokinase by citrate. However, as Warburg noted,<sup>1</sup> many aggressive cancers with abnormal respiration are limited to glycolysis by abnormal mitochondria. The number and kinds of mitochondrial defects in cancers are vast and diverse.<sup>34,35</sup> However, aggressive tumors have been reported with intact TCA enzymes but increased expression of uncoupling protein 2<sup>36</sup> and reduced intracellular ATP (adenosine triphosphate).<sup>37,38</sup> By supplying acetyl CoA and citrate, diet-induced ketosis can further inhibit glycolytic ATP in tumors with mitochondrial abnormalities of this type, reducing the chemical bond energy needed for cancer growth.

- Fatty acid synthase inhibition: Drugs targeting fatty acid synthase have been reported to cause in-

creased apoptosis of breast carcinoma cells.<sup>39,40</sup>

- Fatty acidemia: Long chain fatty acids have been associated with apoptotic changes in a variety of tissues including cancer cells.<sup>41</sup>

- Reduced secretion of insulin and inflammatory cytokines: Hyperglycemia has been associated with overproduction of insulin as well as a pro-inflammatory metabolic environment,<sup>15</sup> including production of reactive oxygen species.<sup>42,43</sup> Inflammatory markers such as C-reactive protein (CRP) and interleukin-6 (IL-6) are factors that have been associated with tumor growth and that are reversed in VLCK. Hypoglycemia itself is associated with increased apoptosis in a variety of in vitro cell culture models<sup>44</sup> and in animal models of brain cancer.<sup>31</sup>

### *Hominid evolutionary adaptation to starvation and ketosis*

Over several million years, the evolution of hominids (hunter-gatherers) was characterized by the occasional protein-rich feast followed by periods when gathered nuts and berries averted starvation.<sup>45,46</sup> It may be inferred that man evolved well adapted to sustained periods of ketosis; but these adaptations are explicit in modern man, who tolerates fasting diets as long as trace elements and hydration are maintained. In short, humans phenotypically lack a dietary requirement for carbohydrate<sup>47</sup> and are well adapted to using fat stores for fuel during periods of starvation.

Agriculture, which permitted a consistent supply of vegetables and grains, dates back no more than 10,000 years and allowed permanent settlements to replace the nomadic hunter-gatherer lifestyle. Prosperity and dietary caloric abundance in the developed world, even among those considered impoverished, are much more recent, arbitrarily noted in the past 100 years.

Although famine continues to

plague humans during war and in underdeveloped regions, it is nonetheless reasonable to suggest that sustained ketosis is not prevalent in the modern developed world. Causes for ketosis are either of short duration (fasting during religious and cultural observances) or, perhaps ironically, are associated with ketogenic or starvation diets in overweight individuals.

#### *Cancer development and evolution*

Irrespective of the initial insult that leads to a cancer phenotype, each cancer evolves within a human organism. Since cancers require approximately 20 to 25 generational doublings before they become clinically detectable, most, regardless of cause, have evolved under conditions of substrate abundance and are therefore unlikely to have experienced metabolic effects common to starvation and the related VLCK dietary state, including ketosis. Cancer's well-known ability to escape many normal metabolic regulatory inhibitions is understood as a product of selective evolutionary pressures favoring these escape mechanisms. However, human beings living in carbohydrate abundance do not provide a metabolic environment of sustained ketosis, which would therefore not be expected to exert selective pressure on most modern cancers.

#### *Hypothesis*

Human beings have successfully adapted to starvation and the related VLCK state. On the other hand, cancers exposed to an *unfamiliar* VLCK state should express a wide range of accidental adaptive survival mechanisms and differential vulnerabilities relative to their host tissues.

In the extreme, the absence of ketotic selective pressure predicts that *all* plausible mechanisms for both vulnerability and adaptation will eventually be expressed. In our current level of ignorance, one may speculate that equal frequencies of vulner-

ability, stable disease, and adaptation to a VLCK diet may be found. Specifically, some cancers are likely to be vulnerable to the ketotic state because this selective pressure is absent in our high carbohydrate world.

Starvation has been used successfully to treat cancers in animal models.<sup>29,31</sup> In a mouse model, fasting (both chronic and intermittent) improves survival and reduces breast tumor size.<sup>29,30</sup> In humans, weight loss improved lymphedema in human breast cancer.<sup>32</sup>

In general, it remains unattractive to attempt starvation diets for human cancers until much more is understood about their benefits and risks. Alternatively, VLCK diets can provide adequate energy and protein to maintain the host while producing many of the metabolic effects of starvation. The possibility that VLCK diets may have antitumor effects has been reported in animal models<sup>9,11,18,31</sup> and in a human case report of two pediatric patients<sup>3</sup>; ketosis has demonstrated antitumor potential in cell culture studies.<sup>11,12</sup> The hypothesis suggests that it is also important and unsurprising to note that ketosis *failed* to inhibit cancers in other animal models.<sup>31,48</sup>

#### **Conclusion and further investigations**

We are exploring the potential of carbohydrate restriction to inhibit cancer growth in susceptible patients. We have presented the protocol for our ongoing clinical feasibility trial, analogous to a phase I drug trial, and a synopsis of the motivating hypothesis. Our hypothesis leads us to speculate that a VLCK diet may stabilize tumor progression or lead to improvement in up to two-thirds of our subjects. If safety, feasibility, and efficacy can be shown, it will be important to find pretreatment markers for cancers to identify those likely to be either vulnerable or resistant to a VLCK diet. Therefore, in parallel with our clinical trial, we are explor-

ing mechanisms in cell culture and will soon expand to animal study. Safety and feasibility will also lead to expanded clinical trials of longer duration and coupling the use of VLCK diets in multimodality therapy and as an adjuvant to standard cancer therapy to improve disease control. We also believe that identification of molecular markers for susceptibility to carbohydrate restriction has the potential to encourage specific drug development.

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