J Nutrition - commentary

Nutritional targeting of cancer cell metabolism in obesity

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PUBMED indexing
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Conflict of Interests:
All authors have no conflicts of interest to disclose

Word count = 1081

List of financial support: JKS is funded by the Wellcome Trust (Grant Number 206453/Z/17/Z).

CDB is supported in part by the Southampton NIHR Biomedical Research Centre.

As the prevalence of obesity continues to rise worldwide, it is becoming increasingly urgent to address the impact that obesity is having in people who have established disease. It is now recognised that obesity is a risk factor for certain cancers [1] and therefore it is important to test whether treating obesity *per se* improves cancer-related outcomes in patients with these specific cancers.

Although it is well established that treating overweight/obesity improves metabolic and cardiovascular risk factors, it is less certain whether treating overweight/obesity benefits cancer-related outcomes in patients who have established cancer. Traditionally, cancer treatment has focused on targeting tumor-specific growth and metastasis. However, there is increasing interest in determining whether treating obesity also benefits patients with cancer. In this issue of the Journal, Caroline Cohen and colleagues turn to a Ketogenic Diet (KD) as a novel approach in the treatment of overweight patients with cancer [2]. These authors report the results of their trial which finds that a ketogenic diet reduces adiposity and insulin in women with ovarian or endometrial cancer; two cancers that are known to be associated with overweight/obesity.

Mammalian cells derive energy (in the form of ATP) not only from oxidation of carbohydrate but also from oxidation of fat and protein. Most tissues utilise all three dietary substrates (carbohydrate, fat and protein) to generate ATP. However, certain organs e.g. brain cannot utilise fat or protein, and use either glucose (as the preferred substrate) or ketone bodies (when there is insufficient dietary glucose available), to generate ATP. In contrast to healthy mammalian cells, and as first described by Otto Warburg in 1925, proliferating cancer cells, tend to generate ATP not from oxidation of carbohydrate, fat or protein, but primarily from anaerobic glycolysis (of glucose) despite the presence of oxygen [1]. This property allows for fast (albeit very inefficient) generation of energy by cancer cells to support their proliferative growth.

Within a normal well balanced diet, dietary carbohydrate content is sufficient to supplement endogenous glucose production, and hepatic generation of ketone bodies (acetoacetate, beta-hydroxybutyrate and acetone) is suppressed. In contrast KDs are low in carbohydrate (< 20 g/day) and rich in fat and/or protein; and for many years there has been interest in using these diets in the

treatment of obesity. KDs contain insufficient carbohydrate to supplement endogeneous glucose production to satisfy daily physiological glucose requirements. Consequently, ketone bodies are generated from hepatic fatty acid oxidation, to provide the necessary substrate (the ketone body acetone) to allow ATP generation in brain.

It has been proposed that KDs may be disadvantageous to cancer cells because:

1. most cancer cells are also unable to metabolize ketone bodies produced from fatty acid metabolism [3].
2. ketone bodies may inhibit cancer cells' glycolytic metabolism, thereby diminishing cellular growth [4].
3. many types of cancer cells lack the capacity to use fat as an energy source, due to their dependence on aerobic glycolysis.

Therefore, KDs theoretically produce an unfavourable environment for cell growth/proliferation in cancer cells; and importantly, for patients with cancer who also have obesity, KDs may also help decrease whole body levels of fat, since KDs promote fatty acid mobilisation from adipose tissue triacylglycerol depots, thus reducing adiposity and maintaining lean mass [5, 6].

Cohen and colleagues performed a 12-week randomised parallel arm trial using two dietary interventions in 45 women with ovarian or endometrial cancer and a range of BMIs $\geq$ 18.5 kg/m^2. The two treatments were: a) the American Cancer Society diet (ACS), containing high levels of fibre, high levels of antioxidants and low levels of both fat and added sugars; and b) a KD (70:25:5% energy from fat ($\geq$125 g/d), protein ($\leq$200 g/d), and carbohydrate ($\leq$20 g/d). The baseline characteristics of the participants in the trial suggested that the two groups did not differ significantly by age, ethnicity, BMI, cancer type, percentage receiving concurrent chemotherapy, number of previous chemotherapy treatments, or time since initial cancer diagnosis. Of the 25 participants on the KD, 20 (80%) achieved the expected level of ketosis (approximately 0.5 mmol/L urinary ketones) and a similar proportion of all participants adhered to their diets (six women dropped out of the study from either diet). Although, total energy intake was not restricted for either the ACS or KD, at the end of the study both groups exhibited reductions in fat mass and importantly maintained lean mass (considering the need to avoid

cancer-associated sarcopenia). After adjustment for baseline measurements, it was the KD group who achieved the greatest reductions in numerous adipose depots. These reductions coincided with significant reductions in fasting insulin levels and C-peptide, and unaltered IGF-1 and IGFBP concentrations.

As acknowledged by the authors, there are a number of limitations that should be considered when attempting to interpret the findings of this study. These include: A) the heterogeneity of the patient group (participants varied according to cancer type, staging of cancer, treatment history, and concurrent chemotherapy status); B) the investigators did not provide the food for participants. Although, this facet of the study design is not ideal when trying to understand whether either diet decreased calorie intake, this aspect of the study design enhances the generalizability of the results to free living individuals with cancer; C) the study design did not include testing the effects of the diets on healthy control participants, which would have allowed for the comparison of the effects of the KD in cancer-free women; and finally, D) the study design did not include a measure of insulin sensitivity.

Given that any form of weight loss requires a reduction in energy intake and/or increased energy expenditure, it is not clear which of these aspects were responsible for the decreased fat mass in these patients. Although calorie intake is notoriously difficult to monitor in a real-world setting, such information is pertinent because it can provide additional clues towards indirect factors such as diet palatability and nauseating effects of concurrent chemotherapy.

Whilst these data are intriguing and provide an important step in considering new complementary approaches to treating obese individuals with cancer, further studies are clearly required to move the field forward. These studies will also need to address key questions such as: what is the impact of a KD on cancer biomarkers, cancer outcomes and modifying/improving treatment responses? Furthermore, it is also important to know that the longer term use of these diets is safe and there is no risk of promoting cancer cachexia. Finally, it is necessary to consider whether it might be desirable to promote a reduction in fat mass in healthy weight individuals with cancer.

Acknowledgments. JKS and CDB both contributed equally to the writing of the commentary.

Both authors have read and approved the manuscript.

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