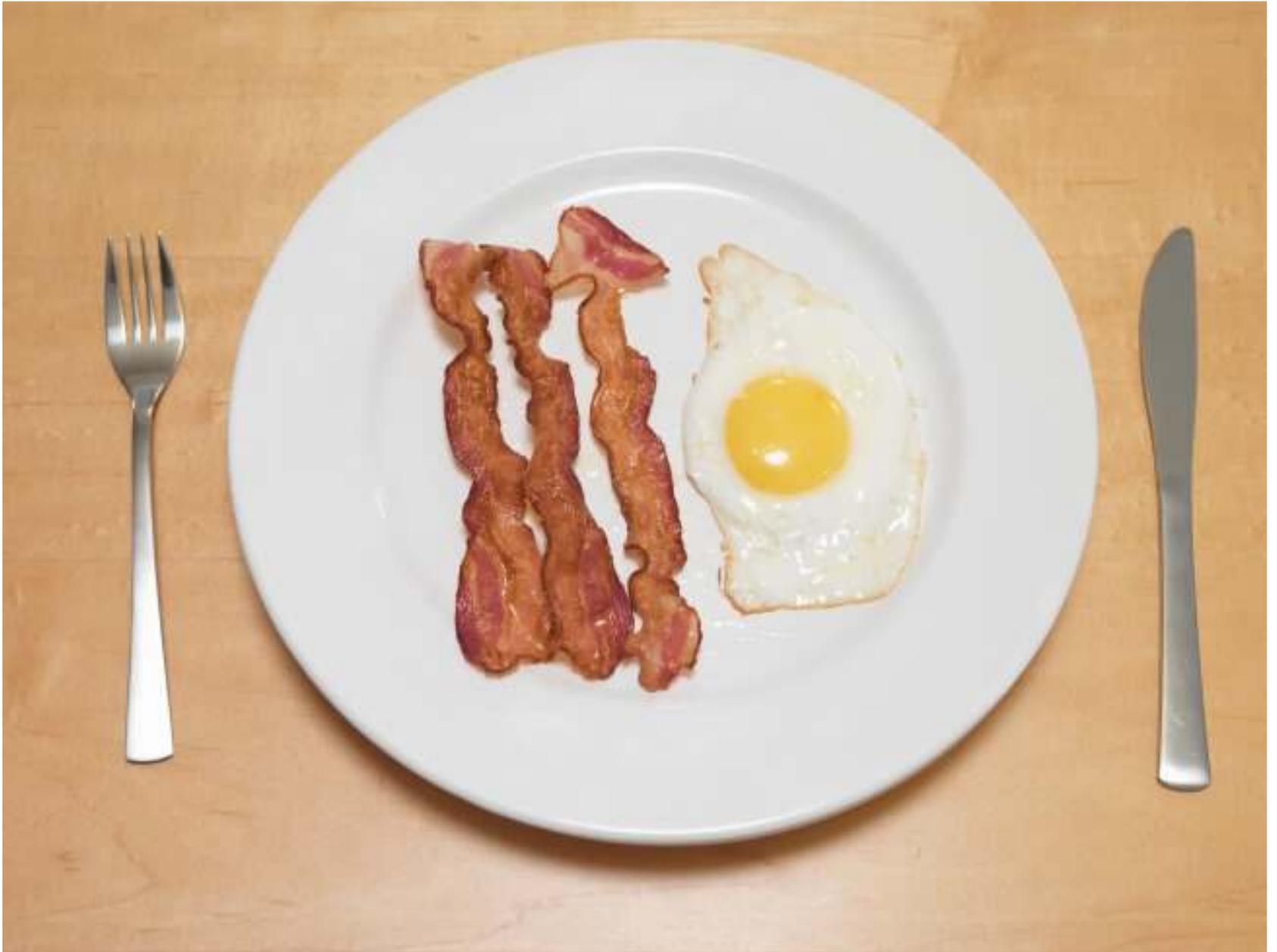


A Ketogenic Diet as an Adjunct to Cancer Treatment

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The rationale for how keto could influence cancer is based on the established differences in glucose metabolism between cancer cells and normal cells.

A ketogenic diet derives approximately 90% of dietary calories from fat, 8% from protein, and just 2% from carbohydrates.¹ In comparison, the standard American diet derives 35%, 15%, and 50% of calories from fat, protein, and carbohydrates, respectively. Although it is rising in popularity, the ketogenic diet is not a new dietary intervention. It is an established nutritional treatment approach — first developed in the 1920s — for patients who have epilepsy that is not well controlled with antiepileptic agents. The keto diet later reemerged as an acceptable intervention in the 1990s.

The ketogenic diet is now being studied as a potential supportive treatment approach in [cancer](#). The rationale is based on the established differences in glucose metabolism between cancer cells and normal cells.

Rationale and Mechanism

Cancer cells demonstrate increased glucose metabolism compared with normal cells, with a shift toward lactic acid production despite the presence of oxygen, a mechanism also referred to as the Warburg effect.^{1,2} Glucose is an important precursor to mitochondrial respiration, which results in the production of energy as ATP. In normal cells, the ultimate conversion of glucose to ATP requires the presence of oxygen; if oxygen is not present, lactic acid is produced. Cancer cells, however, convert glucose to lactic acid in the presence of oxygen.² In addition, cancer cells harbor mitochondrial DNA mutations that result in impaired mitochondrial respiration. Therefore, cancer cells require a large amount of glucose to satisfy their energy needs.

The ketogenic diet is proposed as a potential adjuvant therapy by exploiting these differences between cancer and normal cells. Consuming a ketogenic diet reduces blood glucose levels through a drastic reduction in the amount of carbohydrates consumed.^{1,2} As a result of decreased blood glucose levels, less insulin is secreted, which downregulates signaling pathways that are frequently constitutively active in tumor cells.² Because glucose metabolism is inhibited, energy must be primarily derived from fats.¹ Fat metabolism results in the production of ketone bodies and β -hydroxybutyrate by the liver, which are used to fuel energy production. Cancer cells have difficulty using these pathways because they rely on glucose; the metabolism of fat increases oxidative stress.

Protein metabolism also forces cells to use amino acids rather than glucose to fuel energy production; however, studies suggest that it does not cause the same level of oxidative stress as fat metabolism.¹

Animal Studies

Many animal studies suggest that a ketogenic diet in cancer could have preventive benefits. A meta-analysis of 12 studies that evaluated an unrestricted ketogenic diet compared with a standard high-carbohydrate diet found that the ketogenic diet resulted in decreased tumor growth in animals (hazard ratio [HR], 0.55; 95% CI, 0.27-0.87) and prolonged their mean survival time (HR, 0.85; 95% CI, 0.73-0.97).³

One study that used a mouse model identified a mechanism that suggests a ketogenic diet may help animals overcome resistance to PI3K inhibitors, which have shown disappointingly modest effects as single agents.⁴ PI3K inhibitors target PI3K signaling in cancer cells, but PI3K signaling is also activated in normal cells by insulin. Insulin is secreted as a result of rising blood glucose levels, signaling liver, muscle, and fat cells to uptake glucose. When insulin binds to receptors on these cells, it activates PI3K signaling. However, cancer cells also express insulin receptors; therefore, circulating insulin activates PI3K signaling in these cells as well, resulting in cell proliferation and survival, instead of uptake of glucose. As a result, PI3K inhibitors increase blood glucose levels, further increasing blood insulin levels. Ultimately, this results in resistance to the PI3K inhibitor.

The study found that mice fed a ketogenic diet while treated with a PI3K inhibitor overcame this resistance by lowering blood glucose, thereby reducing blood insulin levels. The result was decreased tumor growth compared with a standard diet. The ketogenic diet was more effective than other blood-glucose–lowering drugs, such as metformin. But, the diet did not affect tumor growth alone.

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Some animal studies have found no effect or a protumor effect associated with the ketogenic diet. For example, a model of tuberous sclerosis complex with kidney cancer demonstrated that the ketogenic diet

promoted tumor growth, as measured by tumor volume.⁵ It is therefore important that future studies evaluate how the ketogenic diet affects different cancer types.

In-Human Studies

The general success of the ketogenic diet in animal models has increased the interest of adopting the diet for patients with cancer.⁶ However, well-controlled studies of the effect of a ketogenic diet on cancer have yet to be completed, although many such studies are under way.

Most in-human data come from case reports and small studies, and though the results are mixed, most studies suggest a potential benefit.

Importantly, all in-human studies to date show that the ketogenic diet is safe, with few adverse events. Most side effects that may occur are transient and mild and include fatigue, constipation, or diarrhea.² One study found that low-density lipoprotein (LDL) cholesterol levels increased after healthy obese adults adopted a ketogenic diet for 6 months.⁷ Another study of the ketogenic diet for epilepsy found similar results, with cholesterol levels progressively rising during 1 year of the diet.¹

Another study reported deficiencies in trace minerals, emphasizing the need to ensure that whole foods are consumed during the diet, and to consider working with a dietician to ensure that micronutrient needs are adequately met. There is also a theoretical risk of kidney damage, though this has not yet been detected in in-human studies.

Conclusions

Preclinical data suggest that the ketogenic diet may be an effective adjunct to cancer treatment, though some cancer types, such as kidney cancer, may not benefit. No in-human studies have found that the ketogenic diet is harmful to patients, even while undergoing conventional treatment, though a rise in cholesterol levels may occur.

Patients who wish to adopt the ketogenic diet should seek the help of a nutritionist to ensure that their micronutrient needs are satisfied and that

they are consuming the appropriate proportions of macronutrients.² Patients may need to supplement their diet with vitamins, minerals, or other micronutrient supplements depending on their dietary patterns or comorbidities.

References

1. Allen BG, Bhatia SK, Anderson CM, et al. [Ketogenic diets as an adjuvant cancer therapy: History and potential mechanism](#). *Redox Biol.* 2014;2:963-970.
2. Klement RJ. [The emerging role of ketogenic diets in cancer treatment](#). *Curr Opin Clin Nutr Metab Care.* 2019;22(2):129-134.
3. Klement RJ, Champ CE, Otto C, Kämmerer U. [Anti-tumor effects of ketogenic diets in mice: a meta-analysis](#). *PLoS ONE.* 2016;11(5):e0155050.
4. Hopkins BD, Pauli C, Du X, et al. [Suppression of insulin feedback enhances the efficacy of PI3K inhibitors](#). *Nature.* 2018;560:499-503.
5. Liśkiewicz AD, Kasprowska D, Wojakowska A, et al. [Long-term high fat ketogenic diet promotes renal tumor growth in a rat model of tuberous sclerosis](#). *Sci Rep.* 2016;6:21807.
6. Weber DD, Aminazdeh-Gohari S, Kofler B. [Ketogenic diet in cancer therapy](#). *Aging (Albany NY).* 2018;10(2):164-165.
7. Chung H-Y, Park YK. [Rationale, feasibility and acceptability of ketogenic diet for cancer treatment](#). *J Cancer Prev.* 2017;22:127-134.