Could ketogenic diet "starve" cancer? Emerging evidence

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ABSTRACT

Cancer cells (CCs) predominantly use aerobic glycolysis (Warburg effect) for their metabolism. This important characteristic of CCs represents a potential metabolic pathway to be targeted in the context of tumor treatment. Being this mechanism related to nutrient oxidation, dietary manipulation has been hypothesized as an important strategy during tumor treatment. Ketogenic diet (KD) is a dietary pattern characterized by high fat intake, moderate-to-low protein consumption, and very-low-carbohydrate intake (<50 g), which in cancer setting may target CCs metabolism, potentially influencing both tumor treatment and prognosis. Several mechanisms, far beyond the originally proposed inhibition of glucose/insulin signaling, can underpin the effectiveness of KD in cancer management, ranging from oxidative stress, mitochondrial metabolism, and inflammation. The role of a qualified Nutritionist is essential to reduce and manage the short and long-term complications of this dietary therapy, which must be personalized to the individual patient for the planning of tailored KD protocol in cancer patients. In the present review, we summarize the proposed antitumor mechanisms of KD, the application of KD in cancer patients with obesity and cachexia, and the preclinical and clinical evidence on KD therapy in cancer.

KEYWORDS

Cachexia; cancer; diet; ketogenic diet; nutrition; nutritionist; obesity

Introduction

Ketogenic diets (KD) had their first clinical applications in the treatment of intractable childhood epilepsy as non-pharmacologic treatment (A D B 1931; Cooder 1933). However, the use of KD was previously documented by French Physicians Guelpa & Marie in 1911 in an article that is considered the basis for the use of KD to mimic fasting as a treatment strategy for epilepsy (Höhn, Dozières-Puyravel, and Auvin 2019; MARIE 1911). KD have been applied for over 80 years as an effective adjuvant therapy in refractory epilepsy (Gasior, Rogawski, and Hartman 2006; Neal et al. 2008). Due to the discovery of diphenylhydantoin, since 1938 the interest for KD declined rapidly, shifting attention onto the new antiepileptic drugs. Consequently, fewer nutritionists were trained to use KD.

Only later, in 1990s the interest for KD was resurged after the treatment of a child with intractable epilepsy, who was successfully treated with a KD (Wheless 2008). In these years, research began to explore the mechanisms, safety, efficacy, and therapeutic actions of KDs for weight loss and to reduce risk for several chronic diseases, such as cancer, obesity, type 2 diabetes, and cardiovascular diseases (Weber, Aminazdeh-Gohari, and Kofler 2018).

Cancer is a major public health problem in worldwide (Siegel, Miller, and Jemal 2019). Although the battle against cancer is mostly based on chemotherapy of latest technologies, there is considerable need for improvement with non-drug therapies, such as KD. This diet therapy, in fact, represents a promising opportunity to modulate the cellular metabolism of cancer cells (CCs) and target their metabolic alterations.

Most of the energy of CCs, even if oxygen is present, comes from glucose. As detailed below, the shift to glycolysis from oxidative phosphorylation is known as the Warburg effect (Warburg 1956). The reduced activity of tricarboxylic acid cycle and of oxidative phosphorylation associated with the increased glycolysis represents one of the metabolic hallmarks of cancer (Hanahan and Weinberg 2011). Recent evidence report the potential beneficial effect of KD in reducing tumor growth, accelerating chemotherapeutic toxicity toward CCs (Klement 2018, 2019b), lowering chronic inflammation (Youm et al. 2015), and protecting

healthy cells from the damage induced by chemotherapy or radiation (Weber et al. 2020). Of interest, KD is far less expensive than anticancer drugs, well tolerated, and fairly easy to implement also for the patients (Klement and Sweeney 2016; Rieger et al. 2014). The dietary manipulation in cancer is a controversial topic in oncology and interest has recently grown in the metabolic features of cancer and the possibility to change them through dietary intervention. In particular, the restriction of dietary energy intake (Lanza-Jacoby et al. 2013; Lin et al. 2013) or the restriction of specific nutrients, including carbohydrates (Caso et al. 2013; Ho et al. 2011) or proteins (Fontana et al. 2013; Lamming et al. 2015), are examples of dietary manipulations influencing growth and key metabolic pathways of cancer.

However, few studies have been performed in humans to evaluate the effect of dietary interventions on cancer pathways so far; thus, murine tumor models have been used as an essential tool to deal with the nutritional management of patients with cancer. In mice models, dietary changes have been reported to protect against the occurrence of cancer and to slow tumor growth after its manifestation (Lv et al. 2014). This mechanism was linked to the reduction of glucose availability, insulin and insulin-like growth factors (IGF)-1 circulating levels (Hursting et al. 2013; Klement and Fink 2016). In this context, the most important anti-tumor effects have been described under fasting condition (Lee et al. 2012), in connection to a rapid increase of ketone bodies concentrations both in humans (Cahill 1976) and mice (Leone, Weinheimer, and Kelly 1999). KDs, which are fasting-mimicking diets, offer a clear advantage in cancer setting, as this dietary pattern leads to production of ketone bodies without the need to restrict energy caloric intake (Klement 2013, 2014).

More recently, KD has been also proposed as a strategy for obesity, leading to a decrease in body weight, chronic inflammation and obesity-related comorbidities, such as metabolic syndrome, type 2 diabetes mellitus (Gupta et al. 2017), and psoriasis, a chronic skin immune-mediated disease which shares with obesity the chronic inflammatory state (Barrea, Megna, et al. 2020).

In particular, through the reduction of carbohydrate intake, KD is able to induce fatty acid mobilization from adipose tissue for the formation of ketone bodies to supply energy to the body, which results in an efficient strategy body weight, chronic inflammation and obesity-related diseases (Paoli 2014). Chronic inflammation, a key mediator of tumorigenesis, is a main feature of obesity, leading to many of its metabolic complications. In addition, obesity-induced inflammation gives additional tumor risk beyond obesity itself (Deng et al. 2016). Obesity is characterized by an increased risk of several cancers, and the clinical management of cancer patients with obesity is generally the same as normal weight patients (Saltiel and Olefsky 2017). Understanding the mechanisms by which obesity drives tumor initiation and progression plays an important role for the development of novel, noninvasive, personalized therapies, including KD, for patients with cancer and obesity. In this context, KD may play an essential role in the concomitant treatment of obesity and cancer.

Despite the dietary modulation by carbohydrate reduction *via* KD has been suggested as an adjuvant therapy to selectively kill CCs, some evidence report that, due to a significant weight loss, KD may exacerbate cancer cachexia (Hae-Yun Chung and Kyoung Park 2017). Cancer cachexia is defined as multi-factorial syndrome, which negatively affects survival, responsiveness to chemotherapy, and quality of life in advanced cancer patients (Sadeghi et al. 2018). However, as reported in most preclinical studies, the process of cancer-induced cachexia can be reversed by KD (Beck and Tisdale 1989; Shukla et al. 2014; Tisdale, Brennan, and Fearon 1987).

In view of the potential beneficial effects of KD on prevention, treatment, and prognosis of cancer in spite of the scarcity of a nutrition-focused review on this topic, and to better define the role of KD in cancer setting, in the present narrative review we summarize the proposed antitumor mechanisms of KD, the application of KD in cancer patients with obesity and cachexia, and the preclinical and clinical evidence on KD therapy in cancer.

Ketogenic diets

An extensive body of evidence exists regarding the metabolic effect of ketones, and recently scientists are focusing on diet-induces ketosis. KD is characterized by a very low carbohydrate content (5-10% of total daily consumed kcal), which contains from 20 to 50 g of carbohydrate per day (Phinney et al. 1983; Yancy et al. 2004). However, it is challenging to define KD since several diets, with significant differences in macronutrients, are defined as KD in the literature. From a pathophysiological standpoint, it is essential to distinguish the diets that can induce ketosis from the diet with reduced content of carbohydrates. Briefly, high-fat KD are based on a restriction of carbohydrates (less than 50 g) with unlimited fat intake and an ad libitum protein intake (Gibson et al. 2015). Initially used for refractory seizures, slightly different varieties are now widely used for weight loss purposes (Gibson et al. 2015), neurological and neuromuscular disorders (Paoli et al. 2014), migraine/headache, metabolic and endocrine disorders like type 2 diabetes, and polycystic ovary syndrome (Gupta et al. 2017), NAFLD (Cunha et al. 2020).

Several KD types are used in clinical practice: the classic ketogenic diet (CKD), the medium-chain triglyceride ketogenic diet (MCTKD) and the modified Atkins diet (MAD). Ketogenic ratio (KR), obtained by the ratio between the grams of fat and the sum of the grams of protein and carbohydrates is commonly used to classify the ketogenic power of diet. The CKD is usually chacterized by a KR of 4:1 (90% of daily calories derive from fat) or 3:1 (87% of daily calories derive from fat). The lipid content is mainly represented by long-chain triglycerides (LCT), whereas protein content depends on the individual requirement. In the MCTKD, 30-60% of the energy derived from medium-chain triglyceride (MCT) oil, which provides a higher ketogenic value than

Table 1. Composition of CKD, MCTKD and VLCKD.

	CKD	MCTKD	VLCKD
Caloric intake	Normo-caloric	Normo-caloric	<800 kcal/d
Carbohydrate (%)	3; 6	20	13
Protein (%)	7; 7	10	43
Fat (%)	90; 87	70	44
Ketogenic Ratio (KR)	4:1; 3:1	Not applicable. MCTs are more efficient to induce ketosis then LCT	Not applicable: fat content is very low
Food items	Vegetable oils (olive oil, coconut oil), nuts (macadamia nut, hazelnut, almond, peanut), fruit (green olives, avocado, coconut), cheeses, fat fish, animal fats, processed meat, eggs, tofu, mayonnaise sauce	Same food used for CKD but with higher content of food with MCTs (Margarine, palm and coconut oils).	Replacement meals (18 g protein, 4 g carbohydrate, 3 g fat with a caloric value of 100–150 kcal).

CKD, classic-ketogenic-diet; KR, ketogenic ratio; MCT, medium-chain-triglyceride; MCTKD, medium-chain-triglyceride-ketogenic-diet; VLCKD, very-low-calorie-ketogenic-diet.

LCT (MCT include caproic (C6), caprylic (C8), capric (C10), and lauric (C12) acids). MAD is characterized by a lower KR than CKD and MCTKD (1:1, 2:1) and a carbohydrate intake of up to 20 g/d.

Another type of KD in the *scenario* is represented by the very low-calorie KD (VLCKD) consisting in very low caloric content (less than 800 kcal per day) and are distinguished by the very-low-calorie diets (VLCD), also thanks to the very low content of carbohydrate (<30–50 g/d, <5–10%), a fixed amount of fats (mainly from olive oil) and a moderate-high amount of protein (1.2–1.4 g/kg of ideal body weight), often supplemented with micronutrients (Caprio et al., 2019; Terzikhan, Doets, and Vonk Noordegraaf-Schouten 2015; Watanabe et al. 2020). In order to achieve a very low caloric content (<800 kcal/d), VLCKD takes advantage of meal replacement, based on high biological value protein preparations.

A specific type of KD should be selected according to the therapeutic aim; VLCKD is mainly used for the treatment of obesity and insulin-resistance, whereas CKD and MCTKD are used for neurological disorders and cancer disease. In particular, high-fat, adequate-protein, and low-carbohydrate dietary treatment is recommended for individuals affected by cancer diseases in order to prevent cachexia. The main differences between CKD, MCTKD and VLCKD are reported in Table 1.

The ketone bodies are defined as organic compounds mainly produced from fatty acid break down by mitochondria of hepatocytes, and, to some extent, also in the heart, gut, kidneys and brain (Guzmán and Blázquez 2004; McGarry and Foster 1980). The free fatty acids released form adipose tissue are transported to the liver where acetyl-CoA form by β-oxidation. The acetyl-CoA under high-glucose levels conditions, is further oxidized to release energy into the tricarboxylic acid cycle and then into the electron transport chain. Differently, in low-glucose conditions the acetyl-CoA oxidated from increased β-oxidation accumulates and challenges the processing capacity of the tricarboxylic acid cycle. Driven by the ketogenic enzymes thiolase and hydroxymethylglutaryl-CoA synthase, respectively, two molecules of acetyl-CoA are used for ketone bodies synthesis (McGarry and Foster 1980). The acetoacetate, β-hydroxybutyrate and acetone are the three main ketone bodies; however, only the first two are important as an energy substrate, and β-hydroxybutyrate is the most abundant ketone body in the blood while acetone that formed spontaneously is further metabolized to pyruvate, lactate, and acetate and breathed off *via* the lungs (Glew 2010). Although small amounts of ketones are synthesized from phenylalanine-tyrosine and in leucine metabolism, the predominant substrates for ketone synthesis are represented by fatty acids (Laffel 1999). Both insulin and glucagon are the key regulators hormones of ketogenesis (McGarry and Foster 1980). In particular, whereas glucagon stimulates ketogenesis, insulin inhibits ketogenesis as it inhibits the hormone-sensitive lipase, reducing lipolysis and the release of free fatty acids, therefore it lowers the substrate of ketogenesis (McGarry and Foster 1980). Finally, insulin inhibits mitochondrial hydroxymethylglutaryl-CoA synthase, which is the rate-limiting step in ketogenesis (Laffel 1999).

Ketone bodies and the ketosis process, while still providing sufficient energy to healthy peripheral tissues, have been hypothesized to inhibit CCs proliferation (Allen et al. 2014; Heiden, Cantley, and Thompson 2009). In addition, both energy caloric restriction and KD, through the inhibition of the IGF-1 pathway, have been found to dramatically decrease CCs proliferation (Klement and Sweeney 2016; Lv et al. 2014). Nevertheless, it is important to emphasize that the degree of weight loss linked to the energy restriction may potentiate cancer-related cachexia (Caccialanza et al. 2018). Beyond the total caloric energy intake, other characteristics of the macronutrient composition are important for the efficacy of KD (Kossoff et al., 2018). Of interest, medium-chain triglycerides, compared to long-chain, because of their ability to passively diffuse through cellular membranes, are more rapidly absorbed from the intestine into the bloodstream and oxidized for energy (Augustin et al. 2018; Ota et al. 2019). In addition, the medium-chain triglyceride have the unique ability to promote in the liver the ketone body synthesis (Page et al. 2009).

Proposed mechanism of action of KD in cancer

Evidence report the use of KD as a potential anti-cancer therapy due to its main ability to suppress glucose/insulin signaling (Abdelwahab et al. 2012; Klement 2019a; Tan-Shalaby 2017; Weber, Aminazdeh-Gohari, and Kofler 2018). Of interest, KD induces widespread hormonal, metabolic,

immune, and genetic modifications in contrast with most tumor therapies that target a single pathway in CCs (Poff et al. 2019; Woolf et al. 2015). Beyond glucose deprivation (Nebeling et al. 1995), further studies reported multiple other mechanisms by which KD may elicit anti-tumor effects (Fine et al. 2009; Magee et al. 1979; Poff et al. 2014; Shimazu et al. 2013; Woolf, Syed, and Scheck 2016; Youm et al. 2015). Several of these effects are directly exerted by ketone bodies, which display important signaling properties in addition to serving as energy substrate (Newman and Verdin 2014). Of interest, ketone bodies have demonstrated intrinsic anti-tumor properties in different tumor subtypes *in vitro* and *in vivo* (Nebeling et al. 1995; Poff et al. 2014; Sawai et al. 2004; Skinner et al. 2009). In 1979, Magee et al. demonstrated the direct anti-cancer effects of ketones. In particular, β-hydroxybutyric acid in a murine melanoma model determined a significant dose-dependent reduction of metastatic spread in lymphoma, cervical cancer, and melanoma cells (Magee et al. 1979). Moreover, Poff et al. demonstrated that viability and proliferation in glioma cells were reduced by physiologic concentrations of β-hydroxybutyric acid despite the presence of high glucose levels (Poff et al. 2014). The anti-cancer effects of ketosis *in vivo* are unknown to date. However, in most preclinical models tested it was suggested an overall beneficial effect (Klement and Sweeney 2016). Nevertheless, it has been reported that ketone bodies introduced without reduction of dietary carbohydrate can lead to tumor growth, acting as an adjunctive energetic substrate in the so called "Reverse Warburg Effect" (Bonuccelli et al. 2010). Furthermore, as reported in more detail below, KD can promote tumor progression in the presence of specific oncogenic mutations that occur in human cancers (Xia et al. 2017).

Glucose dependence, cancer (Warburg effect) and KD

In 1956 Otto Warburg hypothesized that CCs had the ability to increase glycolysis and lactate production independently of the oxygen's presence (Bhattacharya, Mohd Omar, and Soong 2016). In particular, most differentiated cells, in the presence of oxygen, primarily metabolize glucose in the mitochondrial tricarboxylic acid cycle to carbon dioxide by oxidation of glycolytic pyruvate. This reaction leads to the production of nicotinamide adenine dinucleotide hydrogen (NADH), which will be used for the oxidative phosphorylation in the adenosine triphosphate (ATP) production, with minimal production of lactate. On the other hand, differentiated cells produce large amounts of lactate only in conditions of absence of oxygen (anaerobic conditions). In contrast, the metabolism of CCs is often referred to as "aerobic glycolysis" as it produces large amounts of lactate regardless of the availability of oxygen, this condition is referred to as the "Warburg effect" (Warburg 1956).

Despite Warburg originally hypothesized a defect in mitochondria in CCs that leaded to impaired aerobic metabolism, subsequent evidence showed that in most CCs mitochondrial function is not altered (Fantin, St-Pierre, and Leder 2006; Moreno-Sánchez et al. 2007; Weinhouse 1976), thus suggesting an alternative hypothesis for aerobic glycolysis in these cells. From a biochemical point of view, anaerobic glycolysis is much less efficient than aerobic glycolysis. In fact, anaerobic glycolysis produces only 2 ATP molecules per molecule of glucose, while in the oxidative phosphorylation 36 ATP are generated by oxidation of one glucose molecule (Heiden, Cantley, and Thompson 2009). Even if the mitochondrial energy production is a more efficient method, CCs prefer to use glycolytic metabolic pathways to generate energy.

The reasons why a less efficient metabolism in terms of ATP production is preferred for in proliferating cells are essentially two: 1) the inefficient ATP production is a problem only when energy resources are scarce. This is not the situation of the mammalian cells that have available a continual supply of glucose and other nutrients, which reaches the cells through the blood. There is evidence that ATP supply is never limited in these cells, despite the degree of differentiation, cells using aerobic glycolysis also exhibit high ratios of ATP/adenosine diphosphate and NADH/nicotinamide adenine dinucleotide $(NAD)^+$ (Christofk et al. 2008; DeBerardinis et al. 2008). 2) beyond ATP, proliferating cells have other important metabolic requirements directly controlled by signaling pathways involving known oncogenes and tumor suppressor genes (Heiden, Cantley, and Thompson 2009).

In addition, recent studies have shown that increased use of glucose by CCs is an adaptive response to mitochondrial oxidative stress (Bose and Le 2018; Brault and Schulze 2016; Hsu and Sabatini 2008). Therefore, this feature could represent an important target to selectively sensitize CCs to therapies. For example, fasting has been shown to not only improve the response to chemotherapy of healthy tissues, but also to delay tumor growth and sensitize CCs to therapies. In this context, KD is able to affect both glucose metabolism and glucose-related signaling in CCs, compromising energy production and macromolecular synthesis, *via* the reduction of blood level of insulin and IGF-1. Moreover, CCs are inefficient to metabolize toxic substances, such as KB. This allows KD to selectively inhibit the metabolism in CCs and not in normal ones. Furthermore, low level of insulin and IGF-1 decrease the activation of phosphatidylinositol 3-kinase (PI3K)/Akt/mammalian target of the rapamycin (mTOR) system, often over-expressed in CCs, increasing the glucose uptake and up-regulating the membrane translocation of glucose transporters (GLUT) (Unterlass and Curtin 2019).

Because of Warburg effect, glucose from dietary carbohydrates represents a primary metabolic fuel for many cancers and this prompted initial studies into KD as anti-tumor therapy, through the carbohydrate dietary restriction. In fact, in animals and in humans hyperglycemia is known to increases tumor growth rate (Iguchi et al. 1989; Seyfried et al. 2003; Stattin et al. 2007), on the other hand it was observed that KD in humans decrease glucose uptake in CCs by decreasing their glucose availability (Nebeling et al. 1995).

Hyperglycemia, and the subsequent hyperinsulinemia, are associated with an increased risk of several cancer, including breast cancer, pancreatic, colorectal (Boyd 2003; Belfiore and Malaguarnera 2011).

Activation of the insulin receptor stimulates several metabolic pathways, including RAS and MAPK cascade, which promote cell proliferation through the mitogenic effects of insulin, PI3K pathway which promotes cell survival through Akt and mTOR, and nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB) which activates anti-apoptotic and pro-inflammatory pathways (Liang and Slingerland 2003). In addition, also the expression of vascular endothelial growth factor (VEGF), a potent activator of angiogenesis, is induced by insulin (Lu et al. 1999; Miuma et al. 2012). Of interest, KD, by restricting carbohydrate consumption, decreases pancreatic insulin production and increases insulin sensitivity in healthy tissues (Volek and Sharman 2004). Clinical evidence shows that, switching from a standard diet to KD, there is a decrease by 50% of total insulin levels in healthy subjects (Harber et al. 2005), and a 75% increase in insulin sensitivity in type 2 diabetes mellitus (Boden et al. 2005). In a pilot study 10 patients with end-stage cancer receiving KD for 28 days showed a significant reduction of insulin levels ($p = 0.03$), which was negatively associated to the degree of relative ketosis and directly associated to therapeutic response (Fine et al. 2012).

Oxidative stress, cancer and KD

Besides the high glycolysis metabolism, in CCs the pentose phosphate pathway, which oxidizes glucose to produce nicotinamide adenine dinucleotide phosphate hydrogen (NADPH) and ribose-5-phosphate, is increased. NADPH, a co-factor for glutathione/glutathione peroxidase system, is able to reduce hydroperoxides, balancing the reactive oxygen species (ROS) and preventing its potential damages for the cell. This mechanism increasing one-electron reductions of O_2 leads to increased ROS production (Allen et al. 2014). Likewise, energy production by protein leads CCs to produce energy from mitochondrial metabolism with a consequent increase in oxidative stress and ROS production (Jain, Kannan, and Lim 1998; Pelletier and Coderre 2007). The increased oxidative stress and ROS production attributable in part to mitochondrial damage, represents an important phenotype in cancers across tissue types (Fruehauf and Meyskens 2007; Hamanaka and Chandel 2010). In addition, chronic inflammation from sustained hyperglycemia also represents a major source of ROS production in tumors (Fruehauf and Meyskens 2007). The increased ROS production represents a growth advantage for CCs, playing an important role in tumorigenesis and progression (Wiseman and Halliwell 1996). Nevertheless, an up-regulation of endogenous antioxidant systems, maintains at sub-lethal levels the excessive increase of ROS and oxidative stress (Hileman et al. 2004; Portakal et al. 2000). This mechanism allows tumors to survive and differentiate in a redox state, which would be toxic to healthy cells. There is, nevertheless, a limit above which ROS production and oxidative stress irreversibly damage CCs, inducing apoptosis (Kong, Beel, and Lillehei 2000). The ROS production and oxidative stress are a double-edged sword for CCs, which can be used to either inhibit or increase cancer progression (Schumacker 2006). This has spurred development of pro-oxidant therapies with the intention of overcome the threshold point above which ROS and oxidative stress will irreversibly damage the CCs to induce tumoral cell death (Wang and Yi 2008). In fact, radiation, chemotherapy and current non-surgical standard therapies for cancer therapies act in part by enhancing ROS production (Wang and Yi 2008).

The lipid metabolism established by KD, through inhibition of gluconeogenesis to form glucose-6-phosphate necessary to enter the pentose phosphate shunt, decreases the capability of CCs to produce NADPH, thus increasing of the oxidative stress inside CCs (Allen et al. 2014).

Evidence have clearly established that ketosis protects against oxidative stress in healthy tissues, by simultaneously enhancing endogenous antioxidant capacity and decreasing ROS production (Maalouf, Rho, and Mattson 2009; Richard L. Veech 2004). Experimental studies reported that KD lowers basal oxidative stress levels within tumors (Allen et al. 2013; Stafford et al. 2010). Of interest, Stafford et al. examined on a mouse model of glioma fed either KD or standard diet, the effects on gene expression in tumors vs normal brain from animals (Stafford et al. 2010). The authors reported that KD treatment reduced the rate of tumor growth and prolonged survival with a reduction of ROS production in CCs, concluding that KD reduces ROS production and enhances endogenous antioxidant expression in glioma *in vivo* (Stafford et al. 2010).

Mitochondrial metabolism, cancer, and KD

Mitochondria are the fundamental organelle in metabolism and, through the oxidative phosphorylation, represent the production center of a large amount of energy for cells. In fact, through the electron transport chain mitochondria are able to produce energy in the form of ATP. Moreover, mitochondria cooperate to regulate many other functions, related to cell metabolism, cell-cycle control, development, antiviral responses and cell death, etc. (McBride, Neuspiel, and Wasiak 2006). The relation between mitochondrial functions and CCs is an interesting field of research. In fact, CCs, compared to normal ones, show as alterations in mitochondrial metabolism, which is caused by a chronic metabolic oxidative stress, associated to an hypoxic environment within the tumor mass (Xu et al. 2005). However, CCs presented *per se* mitochondrial DNA mutations and alterations in the expression of nuclear encoded mitochondrial proteins, resulting in increased production of ROS during mitochondrial respiration. The rapid growth of CCs requires very high functional mitochondria to support the increased energy expenditure by the cell; thus, oncogenic lesions are likely to modify the metabolism used by mitochondria to sustain tumor growth (De Berardinis and Chandel 2016). These findings have been shown in different tumors, such as ovary, prostate, colon, breast, etc. Mutations in various oncogene, such as K-Ras, Myc, etc., can have an important role in mitochondrial metabolism, trough the increase the metabolism of glucose (see later) and glutamine. Especially glutamine represents a crucial energy form for

mitochondrial functioning; in fact, in some metabolic reprogrammed CCs this amino acid could become "essential" if the cell request is very high. This reprogrammed pathway can assure the energy production and the regeneration of reducing equivalents necessary especially for redox balance (Scalise et al. 2017). Several studies underlined the role of mitochondrial mutations in the increasing levels of ROS and this topic could represent an interesting therapeutically target in cancer (Allen et al. 2014; Chattopadhyay and Roy 2017; De Berardinis and Chandel 2016; Hsu, Tseng, and Lee 2016; McBride, Neuspiel, and Wasiak 2006; Rauckhorst and Taylor 2016).

One of the key characteristics of solid tumors is the oxygen deprivation or hypoxia, which plays an important role in several cellular functions such as cell proliferation, metabolism, survival, angiogenesis, and metastasis (Ruan, Song, and Ouyang 2009). In addition, hypoxia and the subsequent lower pH than normal cells, regulate CCs reducing their response to radiotherapy and the resistance to chemotherapy (Chiche, Brahimi-Horn, and Pouysségur 2010; Eltzschig and Carmeliet 2011; Semenza 2010). In particular, CCs have a proliferation rate higher than the growth rate of new blood vessel generation, therefore newly formed CCs are supplied with lower amount of oxygen; in this way, in order to survive, CCs adapt to the low oxygen environment (Harris 2002). The hypoxia-inducible factor 1 (HIF-1) is the key coordinator mechanism through which CCs adapt and survive in hypoxic condition. HIF-1 is a transcription factor formed by two subunits: the first one HIF-1α, whose expression is regulated by abundance of oxygen, and the second HIF-1β, constitutively expressed (Chattopadhyay and Roy 2017). The expression of HIF-1 is induced by the limited oxygen availability and leads to the regulation of the expression of different genes (Mole et al. 2009). In addition, the expression of HIF-1 is involved in the pathways of angiogenesis, pH regulation, extracellular matrix remodeling, cell death/survival, cell adhesion/migration, cell metabolism, and metastasis (Semenza 2010). From a biochemical point of view, when there is a low availability of oxygen in the cell, pyruvate is mainly converted to lactate instead of acetyl CoA, and the expression of genes involved in the glycolytic pathway is induced by HIF-1. In particular, HIF-1 blocks the function of pyruvate dehydrogenase enzyme resulting in the production of lactate through the expression of pyruvate dehydrogenase kinase 1 (Kim et al. 2006). This increased amount of lactate induces HIF-1, which blocks acetyl-CoA metabolism in the mitochondria, reduces mitochondrial biogenesis and the oxygen consumption (Papandreou et al. 2006; Zhang et al. 2007). Wolf et al. evaluated the effects of KD on various aspects of tumor growth and progression used a mouse model of malignant glioma and found that KD given *ad libitum* significantly reduced the expression of key proteins involved in the hypoxic response that drives tumor growth and progression, including HIF-1α, and NF-κB, and VEGF receptor-2 (Woolf et al. 2015). Finally, KD is transported into the cancer cell through the monocarboxylate transporters, MCTs, which are also responsible for lactate export. The subsequent inhibition of lactate export is able to reduce cancer cells survival (Poff et al. 2014).

The main mechanisms through which KD impair cancer cells are summarized in Figure 1.

Systemic inflammation, cancer and KD

Systemic inflammation, a negative prognostic factor for tumor patients independent of tumor type and stage, is initiated through the acute-phase response by the hepatic tissue in response to cancer or by the secretion of inflammatory cytokines by the cancer itself (Diakos et al. 2014; Greten and Grivennikov 2019), that promotes cancer progression and its invasive capacity (Sowers et al. 2014). In addition, systemic inflammation contributes to the inhibition of the patient's sense of hunger and activation of catabolic pathways, which directly or indirectly leads to the cancer-induced wasting syndrome (cachexia), reducing quality of life in patients with cancer (Baracos et al. 2018; Fearon et al. 2011).

It is also known that systemic inflammation is a central and reversible mechanism through which obesity promotes tumor risk and progression (Iyengar et al. 2016). In fact, patients with obesity have inflamed adipose tissue associated also with immune cell infiltration and remodeling (Iyengar et al. 2016). This local inflamed environment is related to different pathophysiologic modifications that may promote a variety of cancers (Iyengar et al. 2016). In the setting of systemic inflammation, other metabolic diseases may occur, including metabolic syndrome and insulin resistance that operates in concert with local mechanisms of cancer to increase the inflammatory state and promote tumor growth and progression (Iyengar et al. 2016).

The NLRP3 inflammasome, a large intracellular multiprotein signaling complexes, is an important component of the innate immune system that plays a key role in the activation of inflammatory processes in response to pathogens or injury, including cancer (Moossavi et al. 2018).

It was observed that NLRP3 inhibition reduces cancer growth and prolongs survival in mouse models of glioma; in keeping with this, its activation contributes to cancer growth and radiotherapy resistance in these models (Li and Liu 2015). Poff et al. reported that chronic feeding of ketone ester R,S-1,3-butanediol acetoacetate diester decreases inflammatory markers levels in healthy rats (Evans, Cogan, and Egan 2017). Of interest, Youm et al. reported that the assembly of the NLRP3 inflammasome and the cytokine production NLRP3-mediated were directly inhibited by ketone β-hydroxybutyrate (Youm et al. 2015). Evidence in humans (Evans, Cogan, and Egan 2017; Forsythe et al. 2008) report that KD may inhibit progression of cancer and induce cell death in tumors by inhibiting systemic inflammation. In particular, several *in vitro* and *in vivo* studies reported that KD exert an anti-inflammatory effect through the suppression of NLRP3 inflammasome, with the consequent reduction of inflammatory markers in brain cancer (Seyfried et al. 2003), in colorectal cancer (Nakamura et al. 2018), and in glioma (Shang et al. 2018).

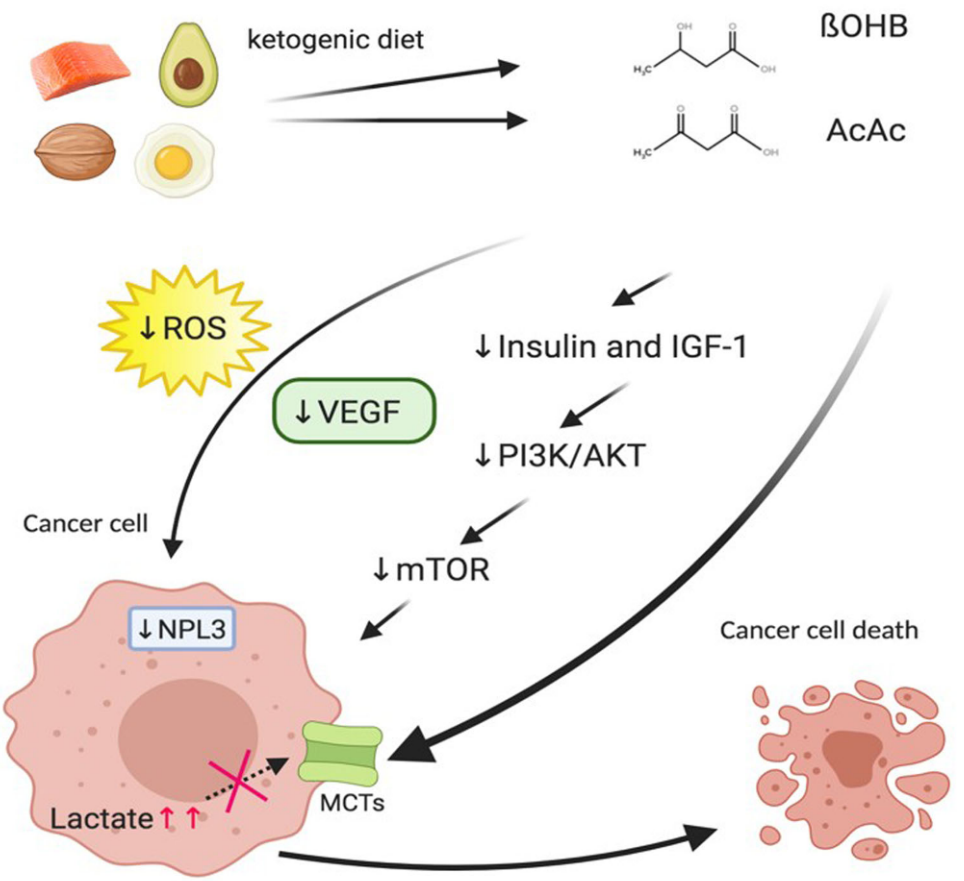

Figure 1. The mechanisms used by ketone bodies to reduce cancer cells survival. Ketogenic diet (KD) induces the synthesis of ketone bodies [beta-hydoxybutyrate (ßOHB) and acetoacetate (AcAc)] by the liver. Ketone bodies (KBs) reduce oxidative species (ROS) production and exert an anti-inflammatory effect through the suppression of NLRP3 inflammasome. KB also reduce plasma level of insulin and IGF-1. Reduced levels of insulin and IGF-1 decrease the activation of phosphatidylinositol 3-kinase (PI3K)/Akt, thereby reducing activation of mTOR, and synthesis of vascular endothelial growth factor (VEGF), a powerful activator of angiogenesis. Finally, KB bind the monocarboxylate transporters (MCTs), which are also responsible for lactate export. The subsequent increase of lactate within cancer cells contributes to reduce their survival.

Of interest, during KD the cancer microenvironment becomes less inflamed (Mulrooney et al. 2011; Seyfried et al. 2019). In fact, KD is anti-inflammatory, anti-angiogenic, and anti-invasive, capable of killing CCs by a pro-apoptotic and anti-inflammatory mechanisms (Simone et al. 2018; Zhou et al. 2007). In particular, β-hydroxybutyrate decreased ROS production through the mitochondrial Co-enzyme Q couple in non-CCs, and simultaneously elevated oxidative stress in CCs (D'Agostino, Olson, and Dean 2009; Seyfried et al. 2017; Veech 2004). Evidence showed that KD can reduce the need for dexamethasone pretreatment, a therapy that can increase availability of glucose levels to the CCs, while also inhibiting chemotherapy-induced apoptosis (Champ et al. 2014; Rieger et al. 2014). Considering that hyperglycemia contributes to rapid breast cancer growth (De Beer and Liebenberg 2014; Wu et al. 2019), KD therapy could reduce both glucose and inflammation levels, thus enhancing the anti-cancer properties of the microenvironment.

Obesity and cancer

Obesity is a well-established risk factor for many chronic diseases such as cardiovascular disease, metabolic syndrome, type 2 diabetes mellitus, nonalcoholic fatty liver disease, and cancer (Vucenik and Stains 2012). The level of the association between cancer and overweight/obesity is very high, since these conditions represent significant factors for the increased incidence of cancer and contribute to 14% of cancer deaths in men and 20% in women (Calle et al. 2003). Cancer incidence will grow with the increasing prevalence of obesity and metabolic syndrome. Furthermore, different studies have report that obesity is a negative independent prognostic factor for different oncological outcomes, such as overall and cancer-specific survival, for different site-specific tumors as well as for all tumors combined (Gallo et al. 2020).

Lifestyle intervention to reduce overweight/obesity, together with smoking cessation, may represent the most effective prevention plan impacting on overall health and cancer prevention (Avgerinos et al. 2019), especially colorectal cancer and post-menopausal breast cancer, which are two of the most common type of cancer worldwide. Many types of tumors have been correlated with excess body weight, the International Agency for Research on Cancer (IARC) Working Group (Lauby-Secretan et al. 2016), stated that there is substantial evidence to affirm that in particular for the post-menopausal breast, endometrial, ovarian, esophageal, colorectal, gallbladder, renal and pancreatic adenocarcinomas, hepatocellular carcinoma, gastric cardia cancer, multiple myeloma, meningioma and thyroid cancers (Altieri et al. 2018; Barrea et al. 2018; Barrea, Fonderico, et al. 2020;

Table 2. Main mechanisms linking obesity and cancer.

Main mechanisms	Main neoplastic action
Abnormalities in the IGF-1 axis/insulin resistance	Inhibition of apoptosis and promotion of cell proliferation, angiogenesis and lymphangiogenesis. The stimulation of the IGF-1 receptor or the insulin receptor, which both have intrinsic tyrosine kinase activity, induces the activation of the downstream transduction through the PI3K-AkT-mTOR pathway, regulator of the cell growth, proliferation and death (Memmott and Dennis, 2009).
Adipose tissue aromatase activity	Excess fat tissue leads to an excess of aromatase activity inducing higher estrogen levels which in turn exert cell proliferation and inhibition of apoptosis in estrogen sensitive organs (mammary tissue and endometrium), *via* IGF-1 production. Progesterone counters estrogen effects inducing the production of IGF-1 binding protein (Shaw et al. 2016).
Oxidative stress and subclinical chronic low-grade inflammation	Mitochondrial and DNA damage induced by increased ROS, tumor necrosis factor-α and interleukin-6, hyperleptinemia and hypoadiponectinemia which contributes to tumor promotion Kasumi and Sato (2019).

IGF, insulin-like growth factor; mTOR, mammalian target of the rapamycin; PI3K, phosphatidylinositol 3-kinase; ROS, reactive oxygen species.

Barrea, Gallo, et al. 2020; Gallo et al. 2019; Laudisio et al. 2018, 2020). A recent review of systematic reviews and meta-analyses aiming to assess the relationship between excess body fat and cancer risk showed that this correlation exists particularly for gastrointestinal tract cancers and, in women, tumors of hormone-sensitive organs (Raglan et al. 2019). Notably, higher fat mass during childhood and early adulthood has been associated with a higher risk of pancreatic cancer and multiple myeloma for women and men, respectively (Avgerinos et al. 2019). Given the increasing incidence of childhood obesity, prevention becomes mandatory.

Interestingly it is acknowledged that an "obesity paradox" also exists in the contest of cancer epidemiology. Obesity correlates with reduced risk of some type of cancers (e.g., head and neck cancers, non-small cell lung cancer, premenopausal breast cancer), and with better outcomes in renal cell cancer, non-small cell lung cancer and metastatic colorectal cancer (Trestini et al. 2018). Possible justifications for this paradoxical effect may be related to methodological factors including the non-informative body mass index (BMI) value as a marker of adipose tissue and/or central adiposity, study limitations involving not appropriate correction for confounding factors (e.g., smoking and age). Particularly smoking, which can be related to lower weight, may represent the explanation to the inverse association between BMI and tobacco-related cancers (Park, Peterson, and Colditz 2018), and importantly, another reverse causality may be explained by the cancer cachexia associated lower weight (Lennon et al. 2016). Given that BMI does not adequately describe the complex relationship between the excess fat mass and cancer, other anthropometric markers have been studied in this direction, such as waist circumference and waist-to-hip ratio. Interestingly, they showed to be better markers than BMI for cancer risk, especially in post-menopausal breast and colon cancer, possibly because they are more strongly associated with visceral fat than BMI (Aleksandrova, Mozaffarian, and Pischon 2018).

Mechanisms underlying the relationship between overweight/obesity and cancer

Although the role of obesity in cancer etiopathogenesis is not fully clarified, several mechanisms have been proposed linking excess body fat and cancer. Recent evidence showed that there is an interplay between excess body fat, insulin resistance, adipocytokines in cancer (Avgerinos et al. 2019). The principal pathways underlying this interplay include the disrupted IGF-1 signaling and insulin-resistance; the adipose tissue aromatase activity; the oxidative stress and subclinical chronic low-grade inflammation; disruption of circadian rhythms and dietary nutrients (Avgerinos et al. 2019) (Table 2).

The role of weight change in cancer risk

Cancer risk may be modulated by both weight gain and weight loss. If BMI *per se* has been associated with several cancer prevalence, adult weight gain, which is a dynamic indicator of adiposity, is also associated with elevated cancer risk of some malignancies (Bandera et al. 2016). On the other hand, intentional weight loss has been associated with reduced risk of some malignancies, in particular, those who are weigh related in women. This effect suggests a role of excess weight in the cancer risk (Birks et al. 2012). Interestingly weight loss has been associated with reduced cancer-related mortality, but this effect needs to be further analyzed (Birks et al. 2012). Weight loss after bariatric surgery represents an interesting setting to observe the effect of weight loss on cancer. Data from recent meta-analysis have shown that subjects undergoing bariatric surgery present a lower risk of obesity-associated cancers and also any type of cancer both in Randomized Controlled Trials (RCT) and non-RCTs (Zhou et al. 2016). Of note, studies from the bariatric surgery setting may be influenced by the short follow-up and higher rate of lost to follow-up.

The role of diet in cancer risk

As for weight gain and weight loss, also diet can both decrease and increase the risk for cancer, and it can be also be used as part of therapy for cancer (Sung et al. 2011). Consistent data showed that frequent consumption of processed meat correlates with higher cancer risk (e.g., renal, stomach, colon, and rectal cancer) (Pischon et al., 2006). On the other hand, higher consumption of fibers is associated with a lower risk of malignancies, such as colorectal cancer (Bingham et al. 2003). Interestingly, subjects with obesity are more used to consume a higher amount of processed meat and less fiber (fruits and vegetables). Fat intake seems to increase breast cancer risk, but the role of fibers on breast cancer risk is unclear. In addition to nutrients, dietary patterns, such as the Mediterranean diet, have been associated

with lower cancer risk (Filomeno et al. 2015), possibly thanks to its high content in fiber and antioxidants.

The role of KD in obesity

KD may represent nutritional strategies for weight loss and cancer prevention thanks to their effect on the reduction of the excess fat mass and insulin resistance (Leidy et al. 2015). However, regarding nutritional support for people with obesity and cancer, although preclinical (Ho et al. 2011; Poff et al. 2013), and some clinical data (Rieger et al. 2014; Schmidt et al. 2011) on the role of KD on tumors exist; strong clinical evidence is still missing. In this direction, the European Society for Clinical Nutrition and Metabolism (ESPEN) guidelines on nutrition in cancer patients, does not recommend KD for patients with cancer, mainly due to the lack of robust evidence-based data from RCT (Arends et al. 2017).

Recently Castellana et al. conducted a systematic review and meta-analysis of twelve studies to evaluate the efficacy and safety of KD in patients with overweight and obesity (Castellana et al. 2020). After four weeks of KD a reduction of anthropometric parameters including body weight (-15.6 kg), BMI (-5.3 kg/m^2), and waist circumference (-12.6 cm), and metabolic profile such as HbA1c (-0.7%), total cholesterol (-28 mg/dl), triglycerides (-30 mg/dl), AST (-7 U/l), ALT (-8 U/l), and GGT (-8 U/l), was observed. Of interest, the weight lost was stable at two years of follow-up ($p = 0.12$). These results supports the use of KD in the management of overweight and obesity as an effective strategy of cardio-metabolic and physical rehabilitation (Castellana et al. 2020).

Similarly, Bueno et al. conduced a meta-analysis aimed to investigate the difference in better long-term body weight and cardiovascular risk factor management comparing VLCKD (<50 g carbohydrates per day) with a conventional low-fat diet (a restricted-energy diet with less than 30% of energy from fat), with 12 months or more of follow-up (Bueno et al. 2013). Patients assigned to VLCKD achieve a greater weight loss compared to patients assigned to a conventional low-fat diet in the long-term, concluding that VLCKD may be an alternative tool against overweight/obesity than a conventional low-fat diet (Bueno et al. 2013).

Cachexia and cancer

Cancer-related cachexia is a multifactorial syndrome characterized by the loss of body weight, mainly consisting of skeletal muscle loss, and with or without fat mass loss. This condition is caused by several factors, including reduced calorie intake and appetite, increased energy expenditure, excess catabolism, and inflammation (Baracos et al. 2018). Of note, if malnutrition can be easily reversed by supplementation of an appropriate amount of nutrients, cachexia can only be partially reversed by nutritional support. Cachexia is associated with increased complications from cancer surgery and mortality (Fearon et al. 2011). Several cancers are more frequently associated with cachexia, including pancreatic, esophageal, gastric, pulmonary, hepatic, and colorectal cancers. Gastrointestinal tract cancers are possibly related to cachexia for their effect on food ingestion, digestion, and absorption; however, cachexia is very common at the later stage of the disease irrespective of cancer site (Amano et al. 2017). Nevertheless, there is variability in the prevalence and severity of cachexia among patients with the same type of cancer (Prado et al. 2013). The nutritional deficit is part of the disease and can be partially prevented. Cachexia can be at least partially reversed through the possible protein anabolic response to feeding exhibited by patients with cancer (van Dijk et al. 2015).

Cachexia and obesity

Cancer cachexia diagnosis is centered on weight loss rate with the consequent low BMI (Fearon et al. 2011). It is widely recognized that patients with lower BMI at the diagnosis have an increased risk of cancer-related morbidity and mortality (Martin et al. 2015). However, people with obesity and cancer can experience a large extent of weight loss without reaching a low absolute BMI (Martin et al. 2015), but with a severe skeletal muscle loss (sarcopenia) (Martin et al. 2013), also in the absence of fat loss, making difficult to detect the skeletal muscle loss. Moreover, patients with breast cancer can develop sarcopenic obesity gaining weight after the diagnosis of cancer but losing muscle mass (Demark-Wahnefried, Campbell, and Hayes 2012).

For this reason, a metabolic-nutritional-behavioral multidisciplinary rehabilitation plays a critical role in the management of obesity in people affected by cancer and it should necessarily include a qualified nutritionist to optimize its effects the optimal (Gilardini et al. 2020).

Nutritional treatment of cachexia

Protein synthesis, which is decreased in cachexia, can be reactivated by increased nutrients intake (van Dijk et al. 2015); this effect underlines the role of reduced food intake in cancer-associated cachexia etiology. Nutritional treatment of cachexia aims to maintain or improve food intake, maintain skeletal muscle mass and physical performance, avoid interruption scheduled anti-cancer treatments, and improve quality of life (Baracos et al. 2018). First-line nutritional treatment in cachexia is the volitional nutrition, which consists in the ingestion of nutrients from normal food and/or oral supplements. The artificial nutrition can be applied when the volitional nutrition cannot fulfill the nutritional needs of the patient, especially in patients in whom the caloric deficit is the principal cause of weight loss (e.g., when oral intake deficit is more than 1200 kcal/d). Artificial nutrition can be enteral (tube feeding) or parenteral (intravenous feeding). Evidence supporting artificial nutrition efficacy in the context of cancer cachexia treatment is lacking. Nevertheless, some evidence in support exists in particular when the severe nutritional deficit is mainly due to the cancer location and/or symptoms (Baracos et al. 2018). Among those above, professional nutritional counseling remains the first-line treatment for cancer cachexia (Baracos et al. 2018). The ESPEN guidelines on nutrition in cancer patients stated,

"the theoretical arguments that nutrients 'feed the tumor' are not supported by evidence related to clinical outcome and should not be used to refuse, diminish, or stop feeding" (Baracos et al. 2018). This position discourages caloric restriction approaches in patients with cancer. When it comes to macronutrient distribution, the ESPEN guidelines recommend a high protein diet based on its effect on muscle protein anabolism in patients with cancer (Baracos 2015). More specifically, the authors suggest that protein intake should be above 1 g/kg/d and, if possible, up to 1.5 g/kg/d. The ESPEN guideline also recommends increasing the ratio of energy from fat to energy from carbohydrates in weight-losing cancer patients presenting insulin-resistance. This recommendation has the intent to increase the energy density of the diet and to decrease the glycemic load (Baracos et al. 2018). Despite this recommendation, some unanswered questions on the effect of high-fat diets on cancer-related outcomes in this specific population remain. This recommendation relies more on pathophysiological arguments, in fact in patients with insulin resistance, fat utilization as an energy source is more effective than glucose (Arcidiacono et al. 2012) and fat mobilization and oxidation in the post-absorptive state is very efficient in weight-stable and weight-losing cancer patients (MacDonald et al. 2015). In the parenteral nutrition regimen, several fat emulsions are available, and in this setting, replacing glucose with fat could bring some beneficial effects (e.g., reduced hyperglycemia-related infections, glucose-related positive water balance) (Lindmark, Eden, and Ternell 1986).

Ketogenic nutritional treatment of cachexia

As previously reported, the ESPEN guidelines on nutrition in cancer patients do not recommend KD for patients with cancer, mainly for lack of strong evidence from clinical trials. Still, the authors also report that this does not go against preferring energy from fat to energy instead of carbohydrates in weight-losing cancer patients also presenting insulin-resistance (Baracos et al. 2018). KD used in patients with cancer usually led to weight loss (Avgerinos et al. 2019), but in cachectic patients, KD induced weight gain and subjects maintained a positive nitrogen balance (Fearon et al. 1988). Data from two case reports have shown that malnourished children with malignant astrocytoma tumors reported weight stabilization and improved nutrient and caloric intake (Nebeling et al. 1995) following and a high fat KD. Some preclinical data aiming to explore the effect of KD on cachexia have been published. Tisdale et al. reported that mice transplanted with adenocarcinoma of the colon (MAC-16), which induce cachexia without affecting food intake, when fed a high fat KD maintained more fat and nonfat weight compared with mice fed with normal non-KD (Tisdale, Brennan, and Fearon 1987). Shukla and colleagues showed that ketone bodies reduced survival in multiple pancreatic CCs lines in mice inducing apoptosis (Shukla et al. 2014). Regarding the safety of KD in patients with cancer, few data on a small number of patients have been reported. Low palatability of KD can lead to insufficient energy intake with possible weight loss (Schmidt et al. 2011). In most cases, low adherence was related to the reduced tolerability of the diet associated with nausea or constipation. The adverse effect of long-term use of KD could cause gastrointestinal pain or kidney stones (Kossoff et al., 2018) are usually associated with the medium-chain triglyceride oils and often mild. One patient reported hyperuricemia and dehydration (Zahra et al., 2017). Also, the adverse effect can be mitigated if KD is used in shorter time frames of radio-chemotherapy (Weber et al. 2020). Some other side effects can occur using KD such as nausea, headaches, constipation, fatigue, appetite loss but could be avoided/reduced when the diet is started slowly and adequately supplemented with minerals and vitamins (Ressel 2002). However, many studies have shown good tolerability of KD and that the use of these nutritional approaches is feasible and safe in cancer patients (Weber et al. 2020).

Studies using the KD in cancer: preclinical and clinical evidence

As already discussed, CCs are characterized by an elevated rate of glucose consumption (Kroemer and Pouyssegur 2008). In order to respond to elevated energy request, CCs show an increased glycolysis and lactate fermentation in the presence of oxygen (Warburg effect) (Warburg 1956). Such metabolic pathway is particularly amplified in cancers with metastasis (Gupta and Massagué 2006). When glucose availability decreases, CCs growth is therefore reduced (Fine et al. 2012). While healthy cells use ketone bodies as an alternative energy substrate when glucose is absent (Veech et al. 2001), CCs are characterized by a mitochondrial dysfunction which prevents ketone bodies use for energy (Weinhouse et al. 1956). Finally, ketone bodies act as veritable signaling molecules, able to alter CCs glycolytic metabolism, thereby inhibiting their growth. For all these reasons, the role of KD has been studied since decades in the context of cancer treatment, both in animal models and human subjects (Klement, Brehm, and Sweeney 2020; Tisdale, Brennan, and Fearon 1987; Weber, Aminazdeh-Gohari, and Kofler 2018, Weber et al. 2020).

Preclinical studies

In 1962, the New York Department of Mental Hygiene noted that two women affected by cervical cancer and metastatic melanoma, respectively, showed a delay in cancer growth after two months of daily hypoglycemic events induced by insulin (Koroljow 1962). Such empirical observation triggered numerous studies on animal models of cancer. Preclinical investigations demonstrated KD as a valuable anticancer therapy, particularly toward brain cancers (Weber et al. 2020). KD with or without calorie restriction delayed the growth of neuroblastoma in CD-1 nude mice (Morscher et al. 2015). Interestingly, neuroblastoma is characterized by low levels of Succinyl-CoA:3-ketoacid coenzyme A transferase (SCOT)-1, the enzyme able to metabolize ketone bodies: for such reason KD supplementation decreased cancer proliferation indexes and increased survival (Morscher et al.

Table 3. Most relevant preclinical studies that evaluated KD in cancer.

Authors	Treatment	Models	Results	Comments
Morscher et al. (2015)	SD *vs* KD with or without calorie-restriction	Neuroblastoma in CD-1 nude mice	Delayed tumor growth and prolonged survival in KD group	Favorable effect of KD with or without calorie restriction
Hao et al. (2015)	3 groups: *ad libitum* KD plus omega-3 fatty acids and MCT; *ad libitum* KD plus LCT; SD	BALB/C nude mice with CCs of colon cancer cell line HCT116.	Tumor growth decreases in MCT and LCT groups	Favorable effect of *ad libitum* KD on tumor growth
Martuscello et al. (2016)	KD vs KD supplemented with MCT and less restricted carbohydrate content (sHFLCgroup)	Glioblastoma cells transplanted in NOD SCID mice	KD and sHFLC inhibit GB cells growth and reduce tumor stem cell expansion	sHFLC diet as a viable and more tolerable alternative to KD.
Aminzadeh-Gohari et al. (2017)	cyclophosphamide in combination with either *ad libitum* LCT-KD or LCT-MCT-KD	Neuroblastoma-bearing mice	LCT-MCT dietary intervention inhibited tumor growth more than LCT-KD	*ad libitum* KD enriched with MCT is more effective than KD with LCT
Xia et al. (2017)	High-fat KD	BRAF V600E-human melanoma cells in xenograft mice	High-fat KD increases tumor growth through acetoacetate	Personalized diets based on specific oncogenic pattern might prevent tumor growth
Hopkins et al. (2018)	PI3K inhibitors with or without KD	Naïve mice bearing KPC allografts in the pancreas	KD reduces insulin release and amplifies the response to PI3K inhibitors	Insulin feedback can be prevented by KD, improving the efficacy of PI3K inhibitors
Kasumi and Sato (2019)	KD *vs* SD	BALB/c mice inoculated with a murine colon adenocarcinoma cell line, with subsequent peritoneal dissemination	In KD group tumor weight remained unchanged. Ascite and anemia decreased. VEGF-A, was lower in KD group.	Favorable effect of KD on global health status and survival
Mukherjee et al. (2019)	Restricted KD and DON	VM-M3 and CT-2A murine models of GB	SD group was not included. KD reduced CCs invasion and proliferation and facilitated action of DON	A synergistic effect of diet/drug combination was observed

DON, 6-diazo-5-oxo-L-norleucine, a glutamine antagonist; GB, glioblastoma; KD, ketogenic diet; KPC, Kras-Tp53-Pdx-Cre; LCT, long-chain triglyceride; MCT, medium-chain triglyceride; NB, neuroblastoma; SD, standard diet; sHFLC, supplemented high-fat low-carbohydrate; VEGF-A, vascular endothelial growth factor A.

2015). In order to prevent weight-loss and cachexia, CD-1 nude mice were fed with *ad libitum* KD during cyclophosphamide therapy, showing a considerable reduction in tumor expansion and improvement in response to chemotherapy (Aminzadeh-Gohari et al. 2017). KD has also been investigated in glioblastoma, a high-grade glioma of the adulthood with median survival of 9-12 months (Fuentes-Raspall et al. 2014). In order to avoid side effects of KD and improve its palatability, a supplemented high-fat low-carbohydrate diet was administrated to NOD/SCID animals (Martuscello et al. 2016). Tumor growth was reduced through inhibition of m-TOR expression, and tumor stem cells proliferation was delayed (Martuscello et al. 2016). In another study, KD has been administrated in combination with 6-diazo-5-oxo-L-norleucine (DON), a glutamine antagonist, in order to strengthen therapeutic efficacy toward glioblastoma (Mukherjee et al. 2019). The synergic action of KD and DON therapy decreased toxicity effects, such as edema, hemorrhage and inflammation, and improved overall mice survival (Mukherjee et al. 2019).

KD composed by 720 g of fat, 30 g of carbohydrate, 150 g of protein has been tested on a malignant mouse astrocytoma (CT-2A) and a malignant human glioma (U87-MG) model (Zhou et al. 2007). 20-methylcholanthrene carcinogen was implanted into the cerebral cortex of mice, inducing astrocytoma, whereas a human glioma cell line (U87-MG) was inoculated in SCID mice, characterized by a genetic immune deficiency that affects their B and T cells. KD significantly reduced tumor growth and extended survival in either models (Zhou et al. 2007). Mitochondrial enzymes β-hydroxybutyrate dehydrogenase and SCOT mRNA were found significantly lower in mouse CT-2A and human U87 brain tumors, supporting the theory of mitochondrial dysfunction (Sawai et al. 2004). Another study confirmed the beneficial effects of KD on male BALB/C with colon cancer, where tumor growth was significantly impaired (Hao et al. 2015).

Interestingly, in a mouse model of peritoneal dissemination, characterized by a very poor prognosis, KD was able to extend survival time and improve health status in mice. In particular, KD reduced VEGF-A, a growth-factor involved in the pathogenesis of ascites, and stimulated blood protein synthesis (Kasumi and Sato 2019). Overall, KD improved mice global health status, reducing ascites, bowel tenderness and preventing anemia, without reducing tumor size.

Finally, KD were able to improve CCs response to PI3K inhibitors. PI3K inhibitors cause transient hyperglycemia inducing compensatory systemic hyperinsulinemia. In some CCs, hyperinsulinemia persists for a long time, negatively impacting the therapeutic outcome. Given that KD reduces insulin release, the response to PI3K inhibitors can be increased in several types of CCs (such as advanced endometrial adenocarcinoma, bladder cancer, breast cancer and acute myeloid leukaemia), when used in combination with KD (Hopkins et al. 2018).

Most relevant preclinical studies discussed in this paragraph are reported in Table 3.

Clinical evidences

As already discussed, the first reports suggesting a therapeutic role for carbohydrate restriction in cancer are long-standing (Koroljow 1962). Most of clinical studies

investigating the effects of KD on cancer have been conducted on patients carrying brain tumors. The clinical efficacy of KD in patients with recurrent glioblastoma has been investigated in the ERGO trial (Rieger et al. 2014). Twenty subjects were fed with an isocaloric KD for 6-8 weeks, and a magnetic resonance imaging was assessed to verify disease status. Three subjects abandoned KD for poor tolerability. Three subjects showed a stable disease at the first follow-up (6 weeks), whereas 17 subjects reported disease progression. Patients with disease progression continued KD and started anti-cancer drugs such as ACNU/teniposide (one patient), bevacizumab alone (4 patients) or bevacizumab in combination with irinotecan (3 patients). The group treated with bevacizumab and KD showed a progression-free survival of 20.1 weeks, significantly longer than experienced by a control group of 28 patients treated only with bevacizumab (Mukherjee et al. 2019). This pilot study strongly suggested that KD should be associated to anti-cancer treatments, such as radiotherapy or anti-angiogenic drugs, in order to increase survival.

KD feasibility and safety were also evaluated in two later studies involving patients with brain tumors; in the first, KD was administered to eleven patients affected by glioblastoma, within 2 weeks before beginning of chemoradiation and during the following 6 weeks (van der Louw et al. 2019). Severe side effects were not reported. Therefore, KD was reconsidered as a valuable tool to improve the success of standard chemoradiation in glioblastoma multiforme treatment (van der Louw et al. 2019). In a more recent study, 12 patients with recent diagnosis of glioblastoma multiforme were randomized into two groups [modified KD (MKD) or medium chain triglyceride KD (MCTKD) and were observed for 3 months] (Martin-McGill et al. 2020). Only four patients completed the study (MCTKD n = 3; MKD n = 1). Five subjects showed adverse events due to hydro electrolytic imbalance. Severe adverse events occurred in three patients, but were not related to diet. Global health status improved in either groups of patients treated with KD, but a shorter nutritional intervention (6-weeks) could have probably been preferable, in order to increase diet compliance (Martin-McGill et al. 2020).

The metabolic changes occurring in the brain during KD were studied by Artzi et al. (2017), who noted an increase in acetone and acetoacetate content in the brain of patients affected by glioblastoma, through proton magnetic-resonance-spectroscopy (1H-MRS) (Artzi et al. 2017). This technique might be useful to understand if human brain increases ketone bodies uptake or decreases their utilization and if KD is an effective therapy in brain cancers.

Cohen et al. were the first to study the role of KD in gynaecological cancers (Cohen et al. 2018). Thirty-one patients were fed with KD for 12 weeks and compared to 26 patients treated with a low-fat, high-fiber diet recommended by the American Cancer Society. Women enrolled were affected by endometrial cancer at stages I-III or ovarian cancer at stages I-IV (Cohen et al. 2018). The study investigated body composition and insulin sensitivity. After 12 weeks, a lower total and android fat mass was reported in patients following KD, while lean mass did not change between groups. KD patients also showed reduced fasting insulin levels and an increased insulin sensitivity (Cohen et al. 2018). Given that, android fat is linked to pro-inflammatory cytokines secretion and worsening of cancer proliferation, fat mass reduction and improvement of insulin sensitivity determine an unfavorable environment for tumor growth.

A previous study investigated body composition in six patients affected by solid tumors who followed KD during radiotherapy (Klement and Sweeney 2016). Diet-related side effects were not reported in patients; fat mass decreased in all patients, while fat free mass was unchanged. Total body water was not modified, but few alterations in extracellular water/intracellular water ratio were observed (Klement and Sweeney 2016). Preservation of lean mass plays a key role for a better performance status and long-term prognosis, especially in cancer patients, where malnutrition and cachexia is common.

Recently, Khodabakhshi et al. confirmed feasibility and safety of KD in patients affected by breast cancer: no severe adverse effects occurred during the study, BMI, body weight, and fat mass were significantly reduced when compared with control group ($p < 0.001$) (Khodabakhshi et al. 2020). KD was shown as an effective tool to improve quality of life, especially in subjects affected by cancers in advanced stage. Except minor side effects, such as constipation, nausea and fatigue, subjects treated with KD reported an improvement in mood and sleep quality (Schmidt et al. 2011). Moreover, subjects with previous rapid disease progression did not experience further worsening of the disease and, in some cases, a partial remission after KD was observed. Importantly, these results were positively associated with ketosis levels (Fine et al. 2012).

Iyikesici assessed 44 metastatic non-small cell lung cancer patients treated with weekly carboplatin/paclitaxel together with KD, hyperbaric oxygen, and hyperthermia (Iyikesici 2019). No side effects were reported and adherence to the combined treatment was very high. After a follow-up period of 3 months, 29 subjects were still alive (65.9%) and mean progression-free survival was extended to 41 months, suggesting that complementary therapy is able to improve the outcome in patients with metastatic non-small cell lung cancer (Iyikesici 2019).

Although growing evidences show that KD improves the quality of life, sometimes patients do not perfectly adhere to the diet, particularly when KD is used in combination with other therapies whose toxicity can potentially amplify diet-related side effects. A previous study evaluated the effects of KD in non-small cell lung cancer or pancreatic cancers patients receiving different oncological treatments (Zahra et al., 2017). Seven non-small cell lung cancer patients (ketolung group) were treated with chemoradiotherapy (carboplatin/paclitaxel 50 mg/m^2 with radiation – 66 Gy/33 fractions) and KD for 6 weeks while two patients affected by pancreatic cancer (ketopan group) received KD and chemoradiotherapy (gemcitabine 600 mg/m^2 with radiation – 50.4 Gy/28 fractions) for 5 weeks. At the end of the combined therapy, patients were monitored for one year. In the ketolung group, only two patients completed the study; four patients showed minor side effects while one patient stopped trial after experiencing asymptomatic hyperuricemia (Zahra et al., 2017). In the ketopan group, one patient experienced

Table 4. Most relevant clinical studies that evaluated KD in cancer.

Trial	Diet duration	Patients enrolled	Adverse effect	Results	Comments
Schmidt et al. (2011)	3 mo	16 patients with advanced metastatic tumors treated with KD	No severe adverse effects	5 patients completed 3 mo of KD and showed improved quality of life.	KD is safe for patients with advanced cancer and improves quality of life
Fine et al. (2012)	28 d	10 patients with advanced solid tumors treated with KD	No serious adverse effect	5 patients completed the trial, 1 patient stopped at day 27, 4 patients stopped at day 26. Patients with higher ketone levels in the plasma showed stable disease or partial remission on PET scan	Carbohydrate restriction appears safe and feasible
Rieger et al. (2014)	6 wk	20 patients with recurrent GB treated only with KD, then with drugs with or without KD	No major adverse effects	Treatment with only KD was associated with progression of disease. Patients treated with KD and bevacizumab showed a PFS longer than patients treated only with bevacizumab (20.1 wk vs 16.1).	KD does not bring clinical benefit when used alone
Klement and Sweeney (2016)	4–6 wk	6 (2 early and 4 advanced stage solid cancer) patients followed a KD regimen during RT/RCT	No adverse diet-related side effects	Patients lost FM and preserved FFM; dietary compliance was good	KD is a tool useful to preserve MM and prevent sarcopenia
Zahra et al. (2017)	5 wk (ketopan group) to 6 wk (ketolung group)	2 pancreatic cancer patients (kepopan) and 7 patients with NSCLC (ketolung) treated with KD + RCT	Asymptomatic hyperuricemia in 1 ketolung patient. Dehydration in 1 ketopan patient. 4 ketolung patients stopped KD for poor tolerability.	The median overall survival in the ketolung subjects who prematurely stopped KD was similar to patients who completed the trial (22 vs 17.7 mo)	Poor dietary compliance. RCT toxicity worsens poor tolerability of KD and susceptibility to adverse events.
Artzi et al. (2017)	From 2 mo to more than 31 mo	9 patients with primary brain tumors; 5 patients following KD, 4 patients following SD	No adverse side effects	1H-MRS was used to evaluate ketone bodies metabolism in patients following a KD	1H-MRS represents a useful tool to verify adherence to a KD and its efficacy
Cohen et al. (2018)	12 wk	31 patients with ovarian cancer randomized in KD group and ACS group.	No adverse diet-related side effects.	KD group had lower total (35.3 vs 38.0 kg, $p < 0.05$) and android (3.0 vs 3.3 kg, $p < 0.05$) FM. FFM did not change between the groups. KD group had lower fasting blood insulin levels (7.6 vs 11.2 μU/mL, $p < 0.01$).	KD preserves FFM and reduces FM. Insulin sensitivity is increased and fasting insulin levels reduced
van der Louw et al. (2019)	14 wk	11 patients with GB fed with KD during standard treatment of RCT.	No severe adverse side effects	Only 6 patients completed the study. Quality of life, neurological functioning, and survival did not change over time.	KD is an useful tool in order to maximize the effect of RCT.
Iyikesici (2019)	Not specified	44 NSCLC patients with distant metastasis received CT, KD, hyperthermia and HBOT	No severe adverse side effects	Overall response rate was good (61.4%); Mean overall survival was 42.9 mo. Control group was missing	KD improves the effect of CT in in metastatic NSCLC
Martin-McGill et al. (2020)	3 mo	12 patients with GB were randomized 1:1 to MKD group or MCTKD group	5 adverse events were due to hydroelectrolytic imbalance. 3 serious adverse events were not related to KD	4 out of 12 patients completed the 3-mo diet (MCTKD n = 3; MKD n = 1). GHS was improved in both groups. The median diet duration was 39 d in both groups.	KD is feasible in patients affected by GB. A 6-wk diet intervention was proposed to increase patient compliance
Iyikesici (2019)	Not specified	Forty-four NSCLC patients with metastasis received chemotherapy plus KD, hyperthermia and hyperbaric oxygen therapy	No adverse diet-related side effects.	A control group was not included. However, overall response rate was good (61.4%) and mean overall survival was 49.2 mo	Chemiotherapy with a KD, hyperther-mia and hyperbaric oxygen therapy improves the outcomes of patients diagnosed with stage IV NSCLC.

(*continued*)

Table 4. Continued.

Trial	Diet duration	Patients enrolled	Adverse effect	Results	Comments
Khodabakhshi et al. (2020)	3 mo	60 patients with locally advanced or metastatic breast cancer in CT randomized in KD group (n = 30) or SD group (n = 30)	No severe adverse effects	BMI, body weight, and FM were decreased in KD group ($p < 0.001$). Survival was higher in KD group	KD is safe and well tolerated in patients with breast cancer

[1]H-MRS, proton magnetic-resonance spectroscopy; ACS, American Cancer Society diet; CT, chemotherapy; FFM, fat-free-mass; FM, fat mass; GB, gliobastoma; GHS, global health status; HBOT, hyperbaric oxygen therapy; KD, ketogenic diet; MCTKD, medium chain triglyceride ketogenic diet; MKD, modified ketogenic diet; MM, muscle-mass; NSCLC, non-small-cell lung cancer; PFS, progression-free-survival; RCT, radiochemotherapy; RT, radiotherapy; SD, standard diet.

dehydration and was excluded from the study, while the other completed the study. However, survival and disease progression did not differ between patients who completed the study or not. This study highlighted poor adherence in patients receiving KD during chemoradiotherapy and suggested to provide KD by Percutaneous Endoscopic Gastrostomy tube in order to reduce diet-related side effects.

The clinical studies reported in this review, summarized in Table 4, revealed several gaps of knowledge which need to be addressed in future studies; most clinical trials involved few patients, and in some cases, a control group was not included. Ketone levels were not always monitored, or were measured in urine, even though blood test is more reliable as a measure of compliance to ketogenic dietary regimens. Notably, these studies proposed several types of KD (e.g. modified-Atkins, medium-chain triglyceride-enriched KD, high-fat low-carbohydrate) based on natural protein or food replacement with or without calorie-restriction. Interestingly, as already shown in pre-clinical studies, KD determines favorable effects on body composition, preserving muscle mass and improving performance status. Importantly, KD displays anti-catabolic effects and has promise to reduce cancer progression. There is indeed urgent need to design proper clinical trials, based on homogeneous patient groups treated with the same type of KD.

In summary, KDs have been shown as safe and potentially effective nutritional tools, and represent a fundamental part of a multi-disciplinary therapeutic and rehabilitation strategy, in order to improve the efficacy of anti-cancer treatments, reduce side effects and increase the quality of life in cancer patients (Klement, Brehm, and Sweeney 2020).

Potential contraindications of KD in cancer

As previously reported, the potential contraindications of KD in patients with cancer come from *in vitro* studies and a few early phase *in vivo* evidence.

In a preclinical model of tuberous sclerosis complex, the rare genetic disorder, Liśkiewicz Arkadiusz et al. evaluated the growth of renal lesions in Eker rats (Tsc2+/-) subjected to *ad libitum* prolonged feeding of KD for 4, 6 and 8 months (Liśkiewicz et al. 2016). Authors demonstrated that especially in its long-term usage, KD leads to excessive growth of renal tumors by recruiting ERK1/2 and mTOR, which is related with oleic acid accumulation and the overproduction of growth hormone (Liśkiewicz et al. 2016). At the same time, the Authors reported the exhaustion of the initial adaptative up-regulation of some protective proteins such as Nrf2, p53 and 8-oxoguanine glycosylase α dependent anticancer mechanisms, were started by KD, suggesting that KD-therapy may be contraindicated in patients with tuberous sclerosis complex (Liśkiewicz et al. 2016). More, KD may also be contraindicated in cancer patients with BRAF V600E mutation for KD therapy (Xia et al. 2017). In fact, in a xenograft mouse model, ketone body acetoacetate selectively has enhanced BRAF V600E mutant-dependent MEK1 activation in human tumors promoting the growth of human melanoma cells expressing this mutation. These findings reveal a pathogenic role of dietary fat taken through KD in BRAF V600E-expressing melanoma, emphasizes the need to design "personalized diets" which in addition to acting on cancer prevention may delay cancer progression based on an patient's specific oncogenic mutation profile (Xia et al. 2017). In addition, the potential short-term side effects of KD are gastrointestinal distress, dehydration, hypoglycemia, lethargy, acidosis, hypomagnesaemia, and elevated free fatty acid concentrations and circulating total cholesterol (Kossoff and Hartman 2012; Kwiterovich et al. 2003), while potential long-term side effects of KD are represented by nephrolithiasis, cardiomyopathy, hyperlipidemia, bone mineral loss, and hypercholesterolemia (Caprio et al., 2019).

Of interest, KD can also be deficient in selenium, vitamin D, zinc, and other vitamin and minerals, it should be noted that these adverse potential side effects can be prevented or corrected if KD is prescribed and followed by a qualified Nutritionist that selects the appropriate patients, if KD is well-formulated adjusted in food choices for each patient and well supplemented with vitamins and minerals. In fact, evidence where KD had been well-formulated in the macronutrients intake, including composition of protein, monounsaturated/saturated fats was associated with a reduction in triglycerides, LDL cholesterol, body fat mass, and a suppression of inflammatory markers, with an increase of HDL cholesterol (Caprio et al., 2019; Volek et al. 2004, 2009).

Therefore, data on safety and efficacy of KD targeting tumors patient individuals continue to remain relatively sparse; and well-designed and rigorous clinical trials to evaluate the effectiveness and safety of KD in cancer setting, are urgently needed.

Conclusion

There is still a considerable debate as to whether KD should be included in the management of cancer. Nevertheless, interventions that slow down or halt progression of cancer in early stages, who use a broad-spectrum approach, targeting multiple signaling pathways, also preventing cancer

comorbidities, including cachexia and obesity, and resulting in fewer side effects, represent a very attractive approach to control cancer. KD therapy could represent a novel, non-toxic, cost-effective adjuvant therapy in patients with cancer, offering a potential tool to exploit the metabolic vulnerabilities of tumors far beyond the originally proposed inhibition of glucose/insulin signaling. To date, there are only few data who examined systematically the effect of KD in cancer prevention and progression. The potential positive role of KD in different form of cancer justify the need for well-designed randomized controlled trial to better elucidate the mechanisms by which KD therapy affects tumor prognosis and survival through the nutritional status. The role of a qualified Nutritionist is essential to reduce and manage the short and long-term complications of this dietary therapy, which must be personalized to the individual patient for the planning of tailored KD protocol in cancer patients.

Abbreviations

ATP	adenosine triphosphate
BMI	body mass index
CC	cancer cell
DON	6-diazo-5-oxo-L-norleucine
ESPEN	European Society for Clinical Nutrition and Metabolism
GLUT	glucose transporters
HIF-1	hypoxia-inducible factor 1
IGF	insulin-like growth factor
KD	ketogenic diet
mTOR	mammalian target of the rapamycin
NAD	nicotinamide adenine dinucleotide
NADH	nicotinamide adenine dinucleotide hydrogen
NADPH	nicotinamide adenine dinucleotide phosphate hydrogen
NF-κB	nuclear factor kappa-light-chain-enhancer of activated B cell
PI3K	phosphatidylinositol 3-kinase
RCT	randomized controlled trial
ROS	reactive oxygen species
SCOT	Succinyl-CoA:3-ketoacid coenzyme A transferase 1
VEGF	vascular endothelial growth factor
VLCD	very-low-calorie diet
VLCKD	very low-calorie ketogenic diet

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