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A REVIEW ON ANTICANCER AND ANTIEPILEPTIC PROPERTIES OF CALORIE RESTRICTED AND KETOGENIC DIET

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Abstract

Calorie restriction (CR) and ketogenic diet (KD) are the dietary regimens that decreases calorie intake without suffering through malnutrition period. CR seems to play an essential role in extending life span and involved in the treatment of various age-related diseases. CR is also concerned with the decrease in adiposity. KD is a low protein, low carbohydrate and high fat diet, appeared as very efficient in the treatment of cancer and glioblastoma multiforme tumor cells. KD was developed in 1921 but now it has been thought to be the most effective anti-cancer therapy and it is also being used as an effective agent for epilepsy patients. Ketone bodies are widely used now-a-days to reverse the adverse effects of radiations and chemotherapy too. This review summarizes the complete history of CR and KD as well as their efficacy role in the treatment of various diseases with respective case studies.

INTRODUCTION

It has been long recognized, aging is the ultimate risk factor for a wider range of diseases such as cancer, neurodegenerative diseases, nephropathy, multiple autoimmune diseases, cardiovascular disease as well as type 2 diabetes [1] and calorie restriction (CR) administration helps to extend the life-span and delays the inception of these age-related diseases [2-4]. Calorie Restriction is a prolong reduction of nutritional energy intake with an approximate estimation of 30% devoid of incurrence of malnutrition, markedly decreases the inflammation with the increase in the metabolic rates in non-obese rodents and humans [4-7]. CR is a nutritional mediation that delays and extends aging that is familiar with deleterious changes in tissues and cells with time and extends health period in varies kind of species [2, 8-10]. CR is involved in the great reduction of adiposity; as a consequence it may be of well repute in the mechanism of CR that gives the endocrine function of adipose tissues. Secretions from white adipose tissue (lipokines & adipokines) effect fuel utilization of peripheral tissues as well as the balancing of energy generation through carbohydrate or lipid sources [11-13]. Yet, it is undiscovered that, how aging has been affecting metabolic integrity of adipose tissues in addition to how it relates to the secretions of systemic monitoring factors. It is evident that from research on rat specie, CR persuades gene expression involved in various aspects of metabolism. A further difference involves, long term severe (40%) CR increases the circulating levels of peptide hormone adiponectin (an adipose tissue-derived hormone) [14, 15], where Adiponectin is concerned with great insulin resistivity and it circulates and activates lipid metabolism in responding tissues [16]. Recently a huge research has been conducted on CR, and its impact on age-related pathologies in rodent models was studied, clinical data taken from unsystematic

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clinical trials and human observations demonstrate that molecular and metabolic changes due to CR in non-obese human were quite similar observed in rodents [17]. Prior studies on Rhesus Monkeys at University of Wisconsin (UOW) & National Institute of Ageing (NIOA) displayed that CR diet is involved in the reduction of tumor rate by 75.5% increases life-span and is more effective than a control diet [18, 19].

As a result of rise in obesity level in modern countries the rise in the occurrence of cardiovascular diseases (CVD) was also seen [20]. CVD is the prominent reason for mortality and illness in Western-Countries [21] and by the end of 2020, 40% of all deceases may occur due to CVD [22]. The effects of CVD are exclusively seen in older inhabitants, resulting in increased levels of mortality and disability [23]. Various risk factors of CVD have been recognized including - hypertension, smoking, dyslipidemia, impaired insulin sensitivity, abdominal obesity and sedentary lifestyle [24]. Obesity is also considered to be an eminent hazard for diabetes (Type-2) and insulin resistance [25]. This kind of insulin resistivity is concerned with lipids accumulation, noticeably in skeletal and liver muscles, and may lead to the progress of Non-Alcoholic Fatty Liver Disease (NAFLD) which acts as an autonomous predictor of CVD and present in nearly 90% of obese people [26-28]. According to previous data diet full of carbohydrates, especially rich in fructose and refined sugars are concerned with various metabolic syndromes [29, 30]. Thus, multiple diet plans have been proposed but through all of them carbohydrate restriction diet is of utmost importance due to its involvement in the reduction of all the features of metabolic syndromes [31-33]. Later on with the arrival of Atkin's book in start 1970s [34], carbohydrate restricted diets have come to be very popular, specifically Ketogenic diets (KD). KD is associated with lesser in carbohydrates, rich in fats and adequate proteins. There are various types of KD that are given below in Table-3 [35-37]. Generally, KD is recognized with a decrease in carbohydrates (average-less than 50 grams per day) and comparatively high in the levels of fats and proteins [38].

Some distinctions may exist alike very low-carbohydrate KD, which is more restricting and less than 30 grams per day (Table-1).

Table 1: Standard conformation of KD in adults (planned for a 2,000 kilo calories diet per day). KD, Ketogenic Diet.

Classical KD	Defined as <130 g carbohydrate per day or <26% of caloric intake by the American Diabetes Association
Modified Atkins Diet	65% caloric intake from fat, 30% protein, 6% carbohydrates
Very low-carbohydrate KD	Carbohydrates < 30 g/day

After some days of feeding by such a restricted carb diet, carbohydrates reserves (Glycogen deposited in skeletal and liver muscles) becomes unable to meet the energy requirements, leading to the production of ketone-bodies in liver, which is used by the central nervous system (CNS) as a substitute energy source to the body [39]. Beside these KD seems to be very operative in seizures treatment [40, 41].

Calorie restriction and cancer

According to recent researches, in exposure to energy-restricted nutritional diet consequences in less glucose reserves and growth factor, IGF-1 [4, 42, 43]. Clinical studies in pancreatic, colon and breast cancer have showed that IGF-1 signaling induces a foremost role in anti-cancer CR's effect [42, 44, 45].

Forty-four former studies have disclosed that anti-tumor effects are greatly engaged with CR in animal models (Table-2) [42, 43, 46-87]. Amongst them, most of the researchers used murine models (43 studies) while one of them used hamster model in his study. The most studied types of cancer were prostate, pancreatic, mammary, hepatic and brain cancers. Ovarian, colonic, intestinal and skin cancers were also

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examined in some of the related studies (1 or 2 studies). Chemical induced models, transplanted models, transgenic models and spontaneous models were applied and 90.9% studies reinforced positive CR's anticancer role even with diverse measurements. CR role on cancer initiation has been studied in thirty studies and its defensive role in cancer initiation was investigated in twenty six studies. Three studies demonstrated the CR role in metastasis on cancer and fourteen of them revealed CR's effect on progression. Tumor incidence in percentage, tumor weight, tumor growth measurements were applied frequently. From these forty-four studies CR is concerned with less weight as compared to control. Six out of these forty-four studies indicated that intermittent caloric restriction (ICR) was more effective than chronic caloric restriction (CCR) as tumor inhibitor [18]

Author (Year)	Model	Tumor	Feeding Regimens	Sample size	Time [a]	Body weights(g)	Major Results	C [b]	Q [c]	S [d]
Engelman 1994	Mice	Mammary, TG[e]	AL[f];CR[g] (4–12w[h]); CR(continuously)	60;24;60	60	42.3; 41.4; 27.8	Tumor incidence(%): 83; 50; 13	+	4	I
Tagliaferro 1996	Rats	Mammary, C[i]	AL; Cyclic CR(1w 33% restriction 3w refeeding)	47;49	16	Cyclic CR<AL	Tumor incidence(%): 54;66	-	4	I
Gillette 1997	Rats	Mammary, C	AL; 20%CR	30;30	20.5	CR<AL	Tumor incidence(%): 23.3; 6.7	+	3	I
Pape-Ansorge 2002	Mice	Mammary, TG	AL; ICR[j](3 weeks 50% CR 3 weeks AL);CCR[k]	32;31;33	80	34.9; 31.1; 28.0	Tumor incidence(%): 37.5; 22.5; 33	+	4	I
Thompson 2004	Rats	Mammary, C	40% CR;AL	54;24	11	162;207	Tumor incidence(%): 59;96	+	4	I
Zhu2005	Rats	Mammary, C	40%CR; 6 week 40%CR 8 day refeeding; AL	30;20;29	7	139;160;191	Tumor incidence(%): 56.7;80;96.6	+	3	I
Cleary2007	Mice	Mammary, TG	ICR(3 weeks 50% CR	39;30;31	80	25/32.5[l];26.2; 31.2	Tumor incidence(%): 15;27;84	+	3	I

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			3 weeks AL);CCR; AL							
Jiang 2008	Rats	Mammary, C	20% CR; 40% CR;AL	30;30;30	>7	150;123;180	Tumor incidence(%):60;23;96	+	4	I
Dogan 2009	Mice	Mammary, TG	ICR(3 weeks 50% CR 3 weeks AL); CCR;AL	52;40;44	64	22.6/26.7;25.1;36	Tumor incidence(%): 11.5;20; 45.5	+	5	I
Phoenix 2010	Mice	Mammary, TP[m]	30%CR; AL	/[n]	>27	/	Tumor volume: CR<AL; Metastases: CR<AL	+	3	P, M
De Lorenzo 2011	Mice	Mammary, TP	40%CR; Normal diet	7;7	9	16.6; 21.6	Wet tumor weight: 1.5; 3.5 g; Metastases: CR<AL	+	4	P, M
Nogueira 2012	Mice	Mammary, TP	30% CR; control diet	15;15	18	29;40	Tumor weight: 0.04;0.39 g	+	4	P
Dunlap 2012	Mice	Mammary, TP	30%CR; AL	20;20	>42	/	Tumor area: CR<AL	+	3	P
Saleh2013	Mice	Mammary, TP	ADF(alternate day feeing); 30% CR; AL	80(total)	6	CR<AL	Tumor growth delay of ADF and CR	+	4	P
Mizuno 2013	Mice	Mammary, TG	CCR; ICR(3 weeks 50% CR 3 weeks AL); AL	36;29;30	>50	CR<AL	Tumor incidence(%): 47; 59; 87	+	4	I
Rogozina 2013	Mice	Mammary, TG	ICR(3 weeks 50% CR 3 weeks AL); CCR; AL	45;45;45	82	CR<AL	Tumor incidence(%): 4.4;52.3;66.7	+	4	I
Boileau 2003	Rats	Prostate, C	AL; 20%CR	194 total	>60	CR<AL	Prostate cancer-free survival: CR<AL	+	4	I
SUTTIE 2005	Mice	Prostate, TG	Late-onset 20% CR[o]; AL	109 total	39	CR<AL (sex-pluck)	CR retard epithelial lesion development	+	3	P

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Kandori 2005	Rats	Prostate, TG	30%CR; control	10; 10	91	389.3; 475.2	Deceased epithelial areas/whole area in CR	+	4	I
McCormic-k2007	Rats	Prostate, C	30%CR; 15%CR; AL	43;42;43	48	CR<AL	Tumor incidence(%):72;64;74	-	4	I
Bonorden2009	Mice	Prostate, TG	ICR(2 weeeks 50% CR 2 weeks AL);CCR; AL	101;79;41	50	27.43/30.89[p];29.16;33.48	Median time to tumor detection (week): 38;35;33	+	4	I
Blando 2011	Mice	Prostate, TG	30%CR;overweight control; diet induced obesity	27;23;23	24	23.9;40.1;44.9	Tumor incidence(%):37;100;100	+	4	I
Galet 2013	Mice	Prostate, TP	40% CR; AL	16;16	>3	CR<AL	Tumor weight:295; 467mg	+	4	P
Seyfried 2003	Mice	Brain, TP	AL; 40%CR	7;6	>2	CR<AL	Tumor dry weight: CR<AL	+	3	P
Shelton 2010	Mice	Brain, TP	60% CR; AL	9-10;9-10	>2	CR<AL	CR reduced the growth and invasion of tumor	+	4	P, M
Mulrooney 2011	Mice	Brain, TP	30%CR; AL	5;4	>14	CR<AL	Tumor weight:: CR<AL	+	4	P
Jiang 2013	Mice	Brain, TP	40%CR; AL	30;30	>14	CR<AL	Tumor weight:: CR<AL	+	3	P
Birt 1997	Hamster	Pancreatic, C	AL; 10%CR; 20%CR; 40%CR	35;35;38;33	102	CR<AL	Tumor incidence: 14;9;13;18	-	4	I
Lashinger 2011	Mice	Pancreatic, TP	30%CR; AL	9;9	11	CR<AL	Tumor weight: CR<AL	+	4	P
Lanza-Jacoby 2013	Mice	Pancreatic, TG	ICR (1 week 50% CR 1 week AL); CCR; AL	31;31;31	44	21.7;21;29.6	Incidence of PanIN-2 or more lesions: 27;40; 70%	+	5	I
James 1994	Mice	Hepatic, S[q]	AL; 40% CR	73;72	144	32.3; 23.5	Tumor incidence(%): 27.4; 4.2	+	4	I
Von Tungein, 1996	Mice	Hepatic, C	AL; 40% CR	46;42	84	CR<AL	Tumor incidence(%): 41.; 0	+	4	I
Van Ginhoven 2010	Mice	Hepatic, TP	30%CR(preoperative);- AL	5;5	24	CR<AL	Hepatic tumor load: reduced by CR	+	3	P
Stewart 2005	Mice	Skin, C	40%CR; AL	32;30	>31	CR<AL	Papilloma incidence: CR<AL	+	3	I
Moore 2012	Mice	Skin, C	30% CR; 15% CR;	26;29;27;25	>50	26.7;35.0;41.4;50	Tumor incidence(%): 57.7;69;92.3;96	+	4	I

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			10 kcal% fat; 60 kcal% fat							
Tomita 2012	Rats	Colonic, C	40% CR; AL	23;23	5	CR<AL	Number of aberrant crypt foci: CR<AL	+	4	I
Harvey 2012	Mice	Colonic, TP	30%CR; AL	30;30	>24	CR<AL	Tumo r volume: CR<AL	+	4	I
Carver 2011	Bird	Ovarian, S	555CR; Full-fed	394;393	2year	1423;1896	Tumor incidence(%): 10.3;33.3	+	4	I
Mai 2003	Mice	Intestinal, TG	AL;40%C R	30;28	9	CR<AL	Polyp numbers: CR<AL	+	3	I
Dunn 1997	Mice	/, TG + C	AL; 20%CR	10;10	22	38;30	Tumor incidence(%):40; 20	+	3	I
Hursting , 1997	Mice	/, S	AL(P53-);40%CR(p53-); AL(p53+); 40%CR(p53+)	28-30/group	132	CR<AL	CR delayed tumor mortality relative to AL	+	4	I
Berrigan 2002	Mice	/, TG	AL; 40%CR; 1 day/ week fast	31-32/group	>48	CR<Fast<AL	Tumor free survival: CR>AL; Fast>AL	+	4	I
Tsao 2002	Mice	/, TG	Control; High fat/low calcium; 30% CR	34;46;16	/	CR< Control	Intestinal tumor incidence(%): 69; 65; 69	-	3	I
Yamaza 2010	Mice	/, TG	30%CR; AL	18;17	>144	CR<AL	Tumor incidence(%): 16.7; 94.1	+	3	I

Abbreviations: [a]Time: Time of study (weeks); [b]C: Conclusion of the study, "+" indicates a positive conclusion and "-" represents a negative conclusion; [c]Q: Quality of the study according to a critical checklist of the Stroke Therapy Academic Industry Roundtable; [d]S: The step(s) of cancer that dietary restriction regimens interfere during the initiation, progression and metastasis of cancer, "I" indicates initiation, "P" indicates progression and "M" indicates metastasis; [e]TG: transgenic; [f]AL: Ad libitum; [g]CR: caloric restriction; [h]w: week; [i]C: Chemical-induced; [j]ICR: Intermittent caloric restriction; [k]CCR: chronic caloric restriction; [l]25/32.5: ICR mice sacrificed at the end of the 12th restriction period/ICR mice sacrificed at 1week after 12th refeeding; [m]TP: transplanted; [n]/: not specified; [o]Late-onset 20%CR: al libitum 20 weeks followed by 20% diet restriction; [p]27.43/30.89: Mice euthanized during restriction/Mice euthanized during AL consumption; [q]S: Spontaneous.

Table-2: CR diet experiments and cancer.

1.1 Caloric restriction and cancer treatment

Pancreas produces and release peptide hormone insulin in respond to hyperglycemia which is associated with the progression of metabolic hormones (adiponectin, leptin and IGF-1), aberrant glucose metabolism, insulin resistance and chronic inflammation [88]. Clinical study proves that high levels of insulin and C-Peptide (breakdown product of pro-insulin) are involved in various types of cancer progression [88, 89]. Elevated insulin levels in circulation leads to the hepatic production of IGF-1, which is acute for the development and growth of many tissues as well as a possible risk of progression of many types of cancer [88, 90, 91]. CR induces a decline in insulin and metabolic hormone (IGF-1) levels in circulation and reduces the glucose

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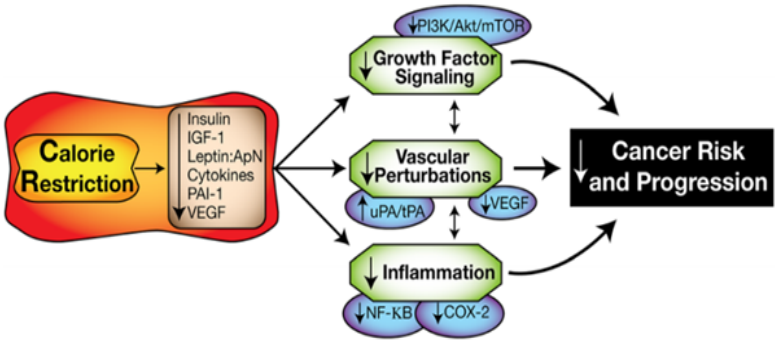
levels as well [90]. Hyperglycemia enforces insulin production and results in hyperinsulinemia which upregulate the GHR (growth hormone receptor) signaling improves IGF-1 production. While CR regimen normalizes the glucose and insulin levels as compared to control diet. Thus, this reduction in glucose due to CR is considered to have anti-cancer effects [7].

As it is evident from past and recent studies on rat models that IGF-1 level in serum constantly declined in proportion to the sternness of CR regimen enforced [74, 77, 92-94] e.g. in rat models CR regimen (25% less in calorie intake) reduces serum IGF-1, results in less cell division and prevents cell leukemia in rats [93]. An overview of CR's effect on cancer is given below in figure-1.



Overview of mechanism: CR and cancer: Chronic exposure with CR regimen minimizes the circulating hormones level as well as the levels cytokines and growth factors, decline in growth factor signaling, rare vascular perturbations with decreased soreness. These responses to CR results in declined risk of cancer and its progression.

Arrow preceding transcript shows a directional effect i.e. concentration or activity.

Abbreviations: IGF-1, insulin-like growth factor-1; ApN, adiponectin; PAI–1, plasminogen activator inhibitor–1; tPA, tissue-type plasminogen activator; uPA, urokinase-type plasminogen activator; VEGF, vascular endothelial growth factor; PI3K, phosphoinositide 3-kinase; mTOR, mammalian target of rapamycin; NF-kB, nuclear factor kB; COX-2, cyclooxygenase-2.

Figure 1

2. Caloric restriction (CR) roles in skin

As we know caloric restriction (CR) is very helpful in preventing many age-related diseases and promotes life-time, improves health-span in a multiple kind species without lacking vital nutrients [95-97]. Most studies on laboratory rodents have showed CR's different metabolic effects on heart, brain, liver, skeletal muscles and on adipose tissues as well. It induces alteration in oxidative phosphorylation, lipid and protein storage and turnover [98].

Even though CR has been exclusively studied in major organs but its metabolic or functional effects on skin was highly neglected in the preceding years. Studies of CR's effect on skin are of quite importance because of its largest size and may also due to its major role as a barrier contrary to dehydration, microbial insults, mechanical trauma and heat loss [99, 100]. Thus, the skin and skin appendages i.e. hair follicles (HF) are expected to be affected in response to CR.

Thus to study CR's effect on skin a research had been conducted using mice with animals houses within the archetypal laboratory conditions, temperature markedly under thermo-neutrality level [101, 102]. Under these specific conditions, animals rested more on their respective insulation capacity, therefore CR studies showed that this dietetic intermediation was effective in the remodeling of fur and skin [101]. A research had been conducted in which mice was calorically restricted for 6 months, enough time-span to investigate several of these metabolic phenotypes concerned with this restricted diet [103]. Consistent with later

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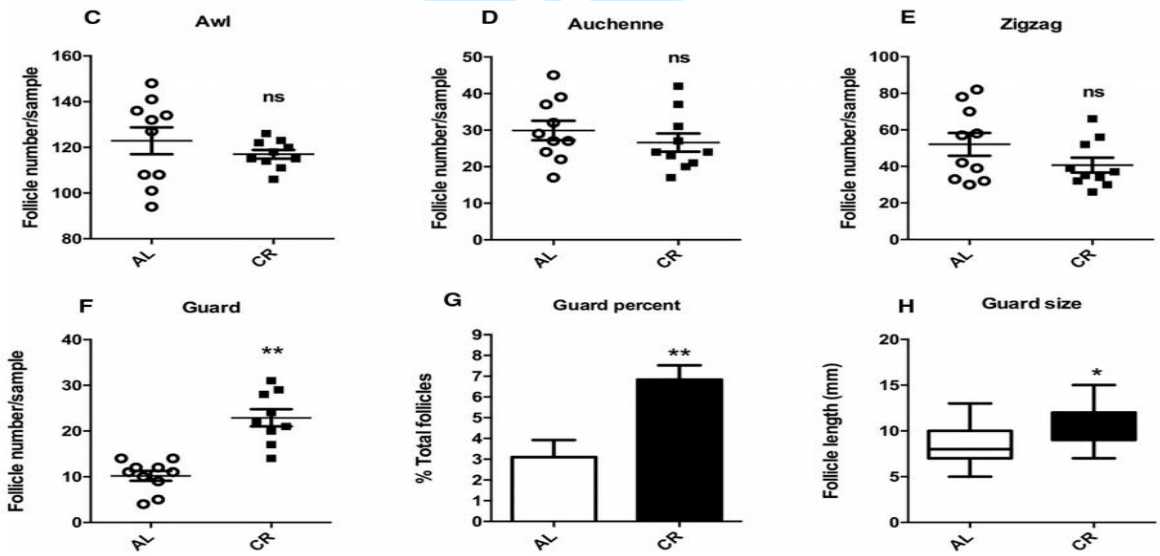
reports [104], mice was observed with the 54% drop in body mass and was substantially smaller than ad libitum (AL) nurtured counterparts. CR animals were also seemed more even, long back and thick (Figure-2).

To appraise the structure of fur coat, 4 kinds of hair follicles were quantified in back skin named as zigzag, awl, guard and auchenne. Awl hairs were shorter and straighter than guard hairs; contained 3 or 4 medulla cell rows [105, 106], their numbers were remained unaltered in CR-fed animals, and however they showed less dispersion amongst CR individuals (Figure 2C). Auchenne hairs were quite similar with awl hairs; except for they had a kink in their hair shaft [105] and were evenly distributed in CR and AL groups (Figure 2D). The similar change was seen in zigzag hairs (Figure 2E). The longest, guard hairs, displayed not kinks and buds off in the course of the first wave of HF, morphogenesis at embryonic-day E13-E14.5 [107] regardless of its low frequency, these hairs displayed highly raised density in CR-fed animals (Figure 2-F;p≤0.001). These hairs reflects a substantial modification

* Of percentage from 2%-4% (in AL animals) to 6%-8% in CR-fed animals (Figure 2-G; p≤0.001) and

* Increase in their hair lengths in CR-fed animals (Figure 2-H; p≤0.05).

Those variations were specific, and were only seen in CR-fed animals and not in AL animals. Consequently, it was proven that in CR-fed animals that they displayed a remodeling in back fur coated coverage. These hair shafts were grown-up by HFSCs (Hair-follicle-stem-cells) [108].



3. Ketogenic diet and Epilepsy

After strokes, epilepsy is the most prominent neurological disorder [109] and affects minimum 50 million individuals all over the world [110]. Despite of a huge advancement in management, diagnosis and anti-epileptic drugs (AED) around 30% of children's are facing uncontrolled seizures and/or insufferable side effects by using AED(s), besides taking restricted chronic treatment options [111]. While, it is probed from past and current data, that KD is widely involved in epilepsy treatment. The ketogenic diet (KD) is a diet consists of sufficient proteins, low carbohydrates and high fat, with effective non-pharmacological treatment for children/adult suffering from refractory epilepsy [112, 113]. Hippocrates established that fasting reduced seizures [112, 114] while the KD's use for the first time was originally described by Russell M. Wilder, in 1921 at Mayo clinic [112, 114]. Then, two French neurologists from the preceding century investigated a decline in seizures in those children/adults who had a four-day fast [115]. Later on Wilder used this data in the development of a diet that induced ketosis as induced by fasting, by using an idea that a diet will be replaced by fasting. However, the study and use of KD was reappeared in the initial

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months of 1990s [114, 116]. For the past two decades the importance of KD was gradually increased and different controlled trials have showed its efficacy in various pediatric seizures population [114]. In general, a prominent reduction (>50%) in seizures was observed in those patients who were initiated with KD [112]. Moreover, patients who have used five or more than five AEDs are subjected to KD [40, 117].

3.1 Ketogenic diet in the treatment of Epilepsy

Despite of the abundant use of KD its specific fundamental mechanism is not yet completely known [115, 118, 119]. While the study on animal models suggests that the fundamental mechanism underlying the treatment of epilepsy with the help of KD is so complicated as it causes change in mitochondrial functions and involves in neurotransmitter release. Mammalian target of rapamycin (mTOR) may also be effected/inhibited by KD [120-122]. In addition to the above there are various theories supporting the fundamental mechanism of KD, one of them are discussed below.

When there is a huge decrease occurs in the consumption of carbohydrates, glucose consumption will correspondingly reduce, resulting in increase in the activity of TCA cycle, increase in γ-aminobutyric acid production in the brain [123], and decrease in glycolysis. Therefore, liver starts to use fatty acids for the production of ketone bodies such as acetoacetate and β-hydroxybutyrate (BHB). Therefore ketone bodies are used to provide energy to cellular metabolism in spite of the use of glucose [124]. Ketone bodies can easily pass through blood brain-barrier and substitutes glucose as a source of energy to induce a condition of ketosis [118, 125]. In the mammalian body a great amount of energy is consumed to fuel neurons. It is scrutinized from the current and past data that in KD fed individuals the raised level of ketone bodies obstruct neuronal excitability, which decreases seizures activity [124, 125]. Studies show ketone bodies affects VGLUT channels via chloride channels on presynaptic glutamate vesicles, and ultimately cause a decrease in glutamate neurotransmitters, helpful in preventing seizures [118]. Since metabolizing enzyme for ketone bodies is found to be abundant in children and infants than in adults. Consequently KD is more effective in infants and children as compared to adults [121].

4. Ketogenic diet and malignant gliomas:

Primary brain tumors arise from different glial cells of the brain and they are categorized on the basis of their aggressiveness at the time of, biopsy [126]. There aggressiveness can be defined in terms of Grades where Grade I and II are slow growing gliomas while Grade III and IV include swiftly growing gliomas. Glioblastoma multiforme (GBM), Grade-IV glioma, is one of the best examples of aggressive glioma yet studied and represents extreme challenges in the administration of cancer patients worldwide. GBM can grow from Grade-I and II gliomas or it can evolve directly [127]. Even with extensive exposure to surgery followed by chemotherapy and radiations, individuals with lately diagnosed GBM have low rate of life expectancy usually 12-18 months and only <10% of them survive to 5 years [128, 129]. GBM develops in the cerebral area of brain and results in progressive memory, neurological deficits and personality disorders. Other symptoms include seizures, nausea and headache. These symptoms vary on the basis of size of the tumor, it may remain asymptomatic until its growth to a massive size and resulted in brain edema. Initial biopsy is subjected to confirm its cellular diagnosis [130, 131].

Ketogenic diet was first used in 1995 by Nebeling et al. for the treatment of Brain malignant tumors [132]. Two female children were diagnosed with stage 4 and stage 3 gliomas respectively, both of which had administered extensive chemotherapy and radiation therapy. The main goal of this study was to check the effects of ketosis on decrease in the availability of glucose interrupt tumor metabolism while maintaining patient's diet status. Both the children responded well to KD and long term tumor management [132].

In 2010, researchers published a case history on a female affected with multicentric GBM. She was treated with restricted ketogenic diet with radiations and chemotherapy. After 2 months on, diet her body weight was lessened by 20% and more prominently no tumor was detected even using either MRI or fluorodeoxyglucose-positron-emission-tomography (FDG-PET). Administration of KD diet was stopped for ten weeks, the tumors was reappeared and

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bevacizumab and CPT11 (irinotecan) chemotherapy was initiated [133]. The patient survived for less than two years after diagnosis. However, this case study demonstrated the positive effects of KD in the treatment of gliomas.

4.1 ketogenic diet and the Treatment of GBM

Calorie restricted KD is a new adjuvant therapy being used for adults suffering with GBM. In 1924, Otto Warburg described the metabolic cause of cancer what we call now "aerobic glycolysis" or "Warburg effect" [134, 135]. Warburg effect describes cancer cells produces energy primarily by non-oxidative breakdown of glucose. RKD therapy is accomplished by implementing 600-1200 kcal/day calorie restricted diet with subsiding protein and carbohydrate consumption whereas increasing fat consumption. The main principle of this therapy is to lowers blood circulating glucose levels to 50-60 mg/dl in order to starve GBM tumor cells while providing enough ketone bodies to meet the energy requirements of the normal cells. Seyfried along with his coworkers have done an experiment on both humans and animals to check the capacity of RKD to adequately lower the blood glucose levels, to suppress the growth of tumor cells [133, 136, 137]. Seyfried divided this therapy in three phases. According to him Phase-1 starts just after the diagnosis of glioma by biopsy and it involves increase in circulation ketone bodies achieved by normally 2-to-3 day's therapeutic fasting (water only). Vitamins and supplements can be supplied to the patients to maintain required energy levels. Phase-2 includes surgical resection of GBM tumors while in most cases patients have already gone through surgical resection. Phase-3 involves long term maintenance of tumors and consists of weeks to cycle from KD to non ketogenic, low glycemic diet [137]. A recent research showed that beside these effects on GBM ketone bodies are also involved in the protection of normal tissues from the hazardous effects associated with chemotherapy and radiations [138].

Classic ketogenic diet

The classic KD, original diet, was developed a century before and at this moment it is taught to be a most rampant type used these days [116]. Maximum classic KD's are designed in the specific proportion (3:1 to 4:1) that fats gives maximum energy as compared to carbohydrates and proteins collectively. Hence, 90% of total calories come from the source of fat in this dietary regimen and the remaining 10% comes from the mutual source of carbohydrates and proteins [115, 118]. Calories are typically limited 80% to 90% in the classic KD according to daily based recommendations for age, and fluid restriction is limited to 90% [139]. The classic KD should be planned considering patient's health condition and must be implemented under the administration of a dietitian and physician [140]. This diet practice is still rare in adults however noticeable results for its efficacy in children's are reported and present in literature [141, 142].

Future Perspective

Calorie restriction and ketogenic diet are the techniques used in the treatment of numerous diseases while in future these dietetic mediations will be useful in the various therapies. CR therapy is engaged with a number of age related disorders but there exact mechanism is not yet elucidated and needs to be discovered in the future [143]. They may coordinate with the other therapies just like in the case of glioblastoma multiforme, KD helps to recover the hazardous effects of chemotherapy and radiations as well as effective agent to repress the growth of tumor cells or direct therapy may also be administered in the case of cancer as described above in the research studies. These dietary mediations will also be useful in the treatment of obesity. More KD results in the decrease in total body weight by 20% in two months while further studies on underlying mechanisms, how obesity is treated with CR are in progress. Many researchers have been subjected this KD on epilepsy patients and its activity is well known in epileptic patients whereas coming years may bring more improvement in the application of KD therapy to epileptic seizures. The development of future-ketogenic-diet may also reduce the side effects of classical ketogenic diet on epileptic patients [118]. Moreover, these mediations will also be quite efficient in Alzheimer's disease, Parkinson's disease and sleep disorders. Further studies on well integrated bio-systems involves

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should momentously facilitate the translation of Calorie Restriction diet into stratagems for the prevention of chronic diseases [144].

Discussion and Conclusion

Calorie restriction and ketogenic diet resembles two characteristics: decrease in carbohydrates and proteins intake, and compensatory increase in ketone-bodies. According to an American Cancer Society, cancer patients who are receiving chemotherapy should increase their protein and caloric intake [145]. Contrary to this view, a reduction in calorie intake by 20%-40% helps in the protection from toxins of chemotherapy and suppresses the growth of tumor cells [144, 146-149]. Based on the ketogenic diet studies and on clinical facts fasting for a shorter period of time should have a positive effect on tumor cells. As I reviewed in by collecting different studies it is obvious that calorie restricted and ketogenic diet is quite effective in tumor cells treatment. Beside these anticancer special effects CR and KD is useful in different other therapies as well. Aforementioned studies demonstrate its efficacy in epilepsy and skin. These are the widely used techniques, not much known yet but it is expected that these mediations will be a part of every single therapy related to age-related disorders.

REFERENCES

1. Heilbronn, L.K. and E. Ravussin, *Calorie restriction and aging: review of the literature and implications for studies in humans.* The American journal of clinical nutrition, 2003. **78**(3): p. 361-369.
2. López-Otín, C., et al., *The hallmarks of aging.* Cell, 2013. **153**(6): p. 1194-1217.
3. Kennedy, B.K., et al., *Geroscience: linking aging to chronic disease.* Cell, 2014. **159**(4): p. 709-713.
4. BERRIGAN, D., et al., *Phenotypic effects of calorie restriction and insulin-like growth factor-1 treatment on body composition and bone mineral density of C57BL/6 mice: implications for cancer prevention.* In Vivo, 2005. **19**(4): p. 667-673.
5. Harvie, M.N., et al., *The effects of intermittent or continuous energy restriction on weight loss and metabolic disease risk markers: a randomized trial in young overweight women.* International journal of obesity, 2011. **35**(5): p. 714.
6. Harvie, M.N., et al., *Intermittent energy restriction induces changes in breast gene expression and systemic metabolism.* Breast Cancer Research, 2016. **18**(1): p. 57.
7. Hursting, S.D., et al., *Calorie restriction and cancer prevention: a mechanistic perspective.* Cancer & metabolism, 2013. **1**(1): p. 10.
8. Anderson, R.M. and R. Weindruch, *Metabolic reprogramming, caloric restriction and aging.* Trends in Endocrinology & Metabolism, 2010. **21**(3): p. 134-141.
9. Omodei, D. and L. Fontana, *Calorie restriction and prevention of age-associated chronic disease.* FEBS letters, 2011. **585**(11): p. 1537-1542.
10. Anderson, R.M., D. Shanmuganayagam, and R. Weindruch, *Caloric restriction and aging: studies in mice and monkeys.* Toxicologic pathology, 2009. **37**(1): p. 47-51.
11. Lago, F., et al., *The emerging role of adipokines as mediators of inflammation and immune responses.* Cytokine & growth factor reviews, 2007. **18**(3-4): p. 313-325.
12. Sethi, J.K. and A.J. Vidal-Puig, *Thematic review series: adipocyte biology. Adipose tissue function and plasticity orchestrate nutritional adaptation.* Journal of lipid research, 2007. **48**(6): p. 1253-1262.
13. Ouchi, N., et al., *Adipokines in inflammation and metabolic disease.* Nature reviews immunology, 2011. **11**(2): p. 85.
14. Combs, T.P., et al., *Sexual differentiation, pregnancy, calorie restriction, and aging affect the adipocyte-specific secretory protein adiponectin.* Diabetes, 2003. **52**(2): p. 268-276.
15. Zhu, M., et al., *Circulating adiponectin levels increase in rats on caloric restriction: the potential for insulin sensitization.* Experimental gerontology, 2004. **39**(7): p. 1049-1059.

Frontier in Medical & Health Research

ISSN: (e) 3007-1607 (p) 3007-1593

16. Turer, A. and P. Scherer, *Adiponectin: mechanistic insights and clinical implications.* Diabetologia, 2012. **55**(9): p. 2319-2326.
17. Most, J., et al., *Calorie restriction in humans: an update.* Ageing research reviews, 2017. **39**: p. 36-45.
18. Lv, M., et al., *Roles of caloric restriction, ketogenic diet and intermittent fasting during initiation, progression and metastasis of cancer in animal models: a systematic review and meta-analysis.* PloS one, 2014. **9**(12): p. e115147.
19. Mattison, J.A., et al., *Caloric restriction improves health and survival of rhesus monkeys.* Nature communications, 2017. **8**: p. 14063.
20. Ng, M., et al., *Global, regional, and national prevalence of overweight and obesity in children and adults during 1980–2013: a systematic analysis for the Global Burden of Disease Study 2013.* The lancet, 2014. **384**(9945): p. 766-781.
21. Murray, C.J. and A.D. Lopez, *Global mortality, disability, and the contribution of risk factors: Global Burden of Disease Study.* The lancet, 1997. **349**(9063): p. 1436-1442.
22. Braunwald, E., *Cardiovascular medicine at the turn of the millennium: triumphs, concerns, and opportunities.* New England Journal of Medicine, 1997. **337**(19): p. 1360-1369.
23. Carbonin, P., et al., *Coronary risk factors in the elderly: their interactions and treatment.* Current pharmaceutical design, 2003. **9**(29): p. 2465-2478.
24. Kannel, W.B., *Cardiovascular risk factors in the elderly.* Coronary Artery Disease, 1997. **8**(8-9): p. 565-575.
25. Koh-Banerjee, P., et al., *Changes in body weight and body fat distribution as risk factors for clinical diabetes in US men.* American journal of epidemiology, 2004. **159**(12): p. 1150-1159.
26. Fabbrini, E., et al., *Intrahepatic fat, not visceral fat, is linked with metabolic complications of obesity.* Proceedings of the National Academy of Sciences, 2009. **106**(36): p. 15430-15435.
27. Fabbrini, E., S. Sullivan, and S. Klein, *Obesity and nonalcoholic fatty liver disease: biochemical, metabolic, and clinical implications.* Hepatology, 2010. **51**(2): p. 679-689.
28. Machado, M., P. Marques-Vidal, and H. Cortez-Pinto, *Hepatic histology in obese patients undergoing bariatric surgery.* Journal of hepatology, 2006. **45**(4): p. 600-606.
29. McKeown, N.M., et al., *Carbohydrate nutrition, insulin resistance, and the prevalence of the metabolic syndrome in the Framingham Offspring Cohort.* Diabetes care, 2004. **27**(2): p. 538-546.
30. Asrih, M. and F.R. Jornayvaz, *Diets and nonalcoholic fatty liver disease: the good and the bad.* Clinical Nutrition, 2014. **33**(2): p. 186-190.
31. Volek, J.S., et al., *Dietary carbohydrate restriction induces a unique metabolic state positively affecting atherogenic dyslipidemia, fatty acid partitioning, and metabolic syndrome.* Progress in lipid research, 2008. **47**(5): p. 307-318.
32. Volek, J.S., et al., *Carbohydrate restriction has a more favorable impact on the metabolic syndrome than a low fat diet.* Lipids, 2009. **44**(4): p. 297-309.
33. Volek, J.S. and R.D. Feinman, *Carbohydrate restriction improves the features of Metabolic Syndrome. Metabolic Syndrome may be defined by the response to carbohydrate restriction.* Nutrition & metabolism, 2005. **2**(1): p. 31.
34. Atkins, R.C. and D.A.D. Revolution, *The High Calorie Way to Stay Thin Forever.* New York: David McKay Inc. Publishers, 1972.
35. Neal, E.G., et al., *A randomized trial of classical and medium-chain triglyceride ketogenic diets in the treatment of childhood epilepsy.* Epilepsia, 2009. **50**(5): p. 1109-1117.
36. Cervenka, M.C. and E.H. Kossoff, *Dietary treatment of intractable epilepsy.* Continuum: lifelong learning in neurology, 2013. **19**(3, Epilepsy): p. 756-766.
37. Pfeifer, H.H., D.A. Lyczkowski, and E.A. Thiele, *Low glycemic index treatment:*

Frontier in Medical & Health Research

ISSN: (e) 3007-1607 (p) 3007-1593

implementation and new insights into efficacy. Epilepsia, 2008. **49**: p. 42-45.

38. Veech, R.L., *The therapeutic implications of ketone bodies: the effects of ketone bodies in pathological conditions: ketosis, ketogenic diet, redox states, insulin resistance, and mitochondrial metabolism.* Prostaglandins, leukotrienes and essential fatty acids, 2004. **70**(3): p. 309-319.
39. Owen, O., et al., *Brain metabolism during fasting.* The Journal of clinical investigation, 1967. **46**(10): p. 1589-1595.
40. Kessler, S.K., et al., *Dietary therapies for epilepsy: future research.* Epilepsy & Behavior, 2011. **22**(1): p. 17-22.
41. Freeman, J.M., E.H. Kossoff, and A.L. Hartman, *The ketogenic diet: one decade later.* Pediatrics, 2007. **119**(3): p. 535.
42. Harvey, A.E., et al., *Decreased systemic IGF-1 in response to calorie restriction modulates murine tumor cell growth, nuclear factor-κB activation, and inflammation-related gene expression.* Molecular carcinogenesis, 2013. **52**(12): p. 997-1006.
43. Lashinger, L.M., et al., *Genetic reduction of insulin-like growth factor-1 mimics the anticancer effects of calorie restriction on cyclooxygenase-2–driven pancreatic neoplasia.* Cancer prevention research, 2011. **4**(7): p. 1030-1040.
44. Nogueira, L.M., et al., *Dose-dependent effects of calorie restriction on gene expression, metabolism, and tumor progression are partially mediated by insulin-like growth factor-1.* Cancer medicine, 2012. **1**(2): p. 275-288.
45. Harvey, A.E., et al., *Calorie restriction decreases murine and human pancreatic tumor cell growth, nuclear factor-κB activation, and inflammation-related gene expression in an insulin-like growth factor-1–dependent manner.* PloS one, 2014. **9**(5): p. e94151.
46. Blando, J., et al., *Dietary energy balance modulates prostate cancer progression in Hi-Myc mice.* Cancer prevention research, 2011. **4**(12): p. 2002-2014.
47. Bonorden, M.J., et al., *Intermittent calorie restriction delays prostate tumor detection and increases survival time in TRAMP mice.* Nutrition and cancer, 2009. **61**(2): p. 265-275.
48. Carver, D.K., et al., *Reduction of ovarian and oviductal cancers in calorie-restricted laying chickens.* Cancer prevention research, 2011. **4**(4): p. 562-567.
49. Cleary, M.P., et al., *Prevention of mammary tumorigenesis by intermittent caloric restriction: does caloric intake during refeeding modulate the response?* Experimental Biology and Medicine, 2007. **232**(1): p. 70-80.
50. De Lorenzo, M.S., et al., *Caloric restriction reduces growth of mammary tumors and metastases.* Carcinogenesis, 2011. **32**(9): p. 1381-1387.
51. Dogan, S., et al., *Effects of chronic vs. intermittent calorie restriction on mammary tumor incidence and serum adiponectin and leptin levels in MMTV-TGF-α mice at different ages.* Oncology letters, 2010. **1**(1): p. 167-176.
52. Dunlap, S.M., et al., *Dietary energy balance modulates epithelial-to-mesenchymal transition and tumor progression in murine claudin-low and basal-like mammary tumor models.* Cancer prevention research, 2012. **5**(7): p. 930-942.
53. Galet, C., et al., *Effects of calorie restriction and IGF-1 receptor blockade on the progression of 22Rv1 prostate cancer xenografts.* International journal of molecular sciences, 2013. **14**(7): p. 13782-13795.
54. Jiang, W., Z. Zhu, and H.J. Thompson, *Dietary energy restriction modulates the activity of AMP-activated protein kinase, Akt, and mammalian target of rapamycin in mammary carcinomas, mammary gland, and liver.* Cancer research, 2008. **68**(13): p. 5492-5499.
55. Jiang, Y.-S. and F.-R. Wang, *Caloric restriction reduces edema and prolongs survival in a mouse glioma model.* Journal of neuro-oncology, 2013. **114**(1): p. 25-32.

Frontier in Medical & Health Research

ISSN: (e) 3007-1607 (p) 3007-1593

56. Kandori, H., et al., *Influence of atrazine administration and reduction of calorie intake on prostate carcinogenesis in probasin/SV40 T antigen transgenic rats.* Cancer science, 2005. **96**(4): p. 221-226.
57. Lanza-Jacoby, S., et al., *Calorie restriction delays the progression of lesions to pancreatic cancer in the LSL-KrasG12D; Pdx-1/Cre mouse model of pancreatic cancer.* Experimental Biology and Medicine, 2013. **238**(7): p. 787-797.
58. McCormick, D.L., et al., *Null effect of dietary restriction on prostate carcinogenesis in the Wistar-Unilever rat.* Nutrition and cancer, 2007. **57**(2): p. 194-200.
59. Mizuno, N.K., et al., *Combination of intermittent calorie restriction and eicosapentaenoic acid for inhibition of mammary tumors.* Cancer prevention research, 2013. **6**(6): p. 540-547.
60. Moore, T., et al., *Energy balance modulates mouse skin tumor promotion through altered IGF-1R and EGFR crosstalk.* Cancer prevention research, 2012. **5**(10): p. 1236-1246.
61. Mulrooney, T.J., et al., *Influence of caloric restriction on constitutive expression of NF-κB in an experimental mouse astrocytoma.* PloS one, 2011. **6**(3): p. e18085.
62. Nogueira, L.M., et al., *Calorie restriction and rapamycin inhibit MMTV-Wnt-1 mammary tumor growth in a mouse model of postmenopausal obesity.* Endocrine-related cancer, 2012. **19**(1): p. 57-68.
63. Phoenix, K.N., et al., *Dietary energy availability affects primary and metastatic breast cancer and metformin efficacy.* Breast cancer research and treatment, 2010. **123**(2): p. 333-344.
64. Rogozina, O.P., et al., *The protective effect of intermittent calorie restriction on mammary tumorigenesis is not compromised by consumption of a high fat diet during refeeding.* Breast cancer research and treatment, 2013. **138**(2): p. 395-406.
65. Saleh, A., et al., *Caloric restriction augments radiation efficacy in breast cancer.* Cell cycle, 2013. **12**(12): p. 1955-1963.
66. Shelton, L.M., et al., *Calorie restriction as an anti-invasive therapy for malignant brain cancer in the VM mouse.* ASN neuro, 2010. **2**(3): p. AN20100002.
67. Stewart, J.W., et al., *Prevention of mouse skin tumor promotion by dietary energy restriction requires an intact adrenal gland and glucocorticoid supplementation restores inhibition.* Carcinogenesis, 2005. **26**(6): p. 1077-1084.
68. Suttie, A.W., et al., *An investigation of the effects of late-onset dietary restriction on prostate cancer development in the TRAMP mouse.* Toxicologic pathology, 2005. **33**(3): p. 386-397.
69. Thompson, H.J., et al., *Effect of dietary energy restriction on vascular density during mammary carcinogenesis.* Cancer research, 2004. **64**(16): p. 5643-5650.
70. Tomita, M., *Caloric restriction reduced 1, 2-dimethylhydrazine-induced aberrant crypt foci and induces the expression of Sirtuins in colonic mucosa of F344 rats.* Journal of carcinogenesis, 2012. **11**.
71. Van Ginhoven, T.M., et al., *Preoperative dietary restriction reduces hepatic tumor load by reduced E-selectin-mediated adhesion in mice.* Journal of surgical oncology, 2010. **102**(4): p. 348-353.
72. Yamaza, H., et al., *FoxO1 is involved in the antineoplastic effect of calorie restriction.* Aging cell, 2010. **9**(3): p. 372-382.
73. Zhu, Z., et al., *Effects of dietary energy repletion and IGF-1 infusion on the inhibition of mammary carcinogenesis by dietary energy restriction.* Molecular Carcinogenesis: Published in cooperation with the University of Texas MD Anderson Cancer Center, 2005. **42**(3): p. 170-176.
74. Berrigan, D., et al., *Adult-onset calorie restriction and fasting delay spontaneous tumorigenesis in p53-deficient mice.* Carcinogenesis, 2002. **23**(5): p. 817-822.
75. Birt, D.F., et al., *Dietary energy restriction does not inhibit pancreatic carcinogenesis by N-nitrosobis-2-(oxopropyl) amine in the Syrian hamster.* Carcinogenesis, 1997. **18**(11): p. 2107-2111.

Frontier in Medical & Health Research

ISSN: (e) 3007-1607 (p) 3007-1593

76. Boileau, T.W.-M., et al., *Prostate carcinogenesis in N-methyl-N-nitrosourea (NMU)-testosterone-treated rats fed tomato powder, lycopene, or energy-restricted diets.* Journal of the National Cancer Institute, 2003. **95**(21): p. 1578-1586.

77. Dunn, S.E., et al., *Dietary restriction reduces insulin-like growth factor I levels, which modulates apoptosis, cell proliferation, and tumor progression in p53-deficient mice.* Cancer research, 1997. **57**(21): p. 4667-4672.

78. Engelman, R.W., N.K. Day, and R.A. Good, *Calorie intake during mammary development influences cancer risk: lasting inhibition of C3H/HeOu mammary tumorigenesis by peripubertal calorie restriction.* Cancer research, 1994. **54**(21): p. 5724-5730.

79. Gillette, C.A., et al., *Energy availability and mammary carcinogenesis: effects of calorie restriction and exercise.* Carcinogenesis, 1997. **18**(6): p. 1183-1188.

80. Hursting, S.D., et al., *Calorie restriction induces a p53-independent delay of spontaneous carcinogenesis in p53-deficient and wild-type mice.* Cancer research, 1997. **57**(14): p. 2843-2846.

81. James, S.J. and L. Muskhelishvili, *Rates of apoptosis and proliferation vary with caloric intake and may influence incidence of spontaneous hepatoma in C57BL/6× C3H F1 mice.* Cancer research, 1994. **54**(21): p. 5508-5510.

82. Mai, V., et al., *Calorie restriction and diet composition modulate spontaneous intestinal tumorigenesis in ApcMin mice through different mechanisms.* Cancer research, 2003. **63**(8): p. 1752-1755.

83. Pape-Ansorge, K.A., et al., *Effect of moderate caloric restriction and/or weight cycling on mammary tumor incidence and latency in MMTV-Neu female mice.* Nutrition and cancer, 2002. **44**(2): p. 162-168.

84. Seyfried, T., et al., *Role of glucose and ketone bodies in the metabolic control of experimental brain cancer.* British journal of cancer, 2003. **89**(7): p. 1375.

85. Tagliaferro, A.R., et al., *Cyclic food restriction alters substrate utilization and abolishes protection from mammary carcinogenesis in female rats.* The Journal of nutrition, 1996. **126**(5): p. 1398-1405.

86. Tsao, J.-L., et al., *Diet, cancer and aging in DNA mismatch repair deficient mice.* Carcinogenesis, 2002. **23**(11): p. 1807-1810.

87. Von Tungeln, L.S., et al., *Inhibitory effect of caloric restriction on tumorigenicity induced by 4-aminobiphenyl and 2-amino-1-methyl-6-phenylimidazo-[4, 5-b] pyridine (PhIP) in the CD1 newborn mouse bioassay.* Cancer letters, 1996. **104**(2): p. 133-136.

88. Pollak, M., *The insulin and insulin-like growth factor receptor family in neoplasia: an update.* Nature Reviews Cancer, 2012. **12**(3): p. 159.

89. Hursting, S.D. and N.A. Berger, *Energy balance, host-related factors, and cancer progression.* Journal of Clinical Oncology, 2010. **28**(26): p. 4058.

90. Gallagher, E., et al., *The pathway from diabetes and obesity to cancer, on the route to targeted therapy.* Endocrine Practice, 2010. **16**(5): p. 864-873.

91. Price, A.J., et al., *Insulin-like growth factor-I concentration and risk of prostate cancer: results from the European Prospective Investigation into Cancer and Nutrition.* Cancer Epidemiology and Prevention Biomarkers, 2012. **21**(9): p. 1531-1541.

92. Weindruch, R. and R.L. Walford, *Retardation of aging and disease by dietary restriction*. 1988: CC Thomas.

93. Hursting, S.D., et al., *The growth hormone: insulin-like growth factor 1 axis is a mediator of diet restriction-induced inhibition of mononuclear cell leukemia in Fischer rats.* Cancer research, 1993. **53**(12): p. 2750-2757.

94. Ruggeri, B.A., et al., *Caloric restriction and 7, 12-dimethylbenz (a) anthracene-induced mammary tumor growth in rats: alterations in circulating insulin, insulin-like growth factors I and II, and epidermal growth factor.* Cancer research, 1989. **49**(15): p. 4130-4134.

Frontier in Medical & Health Research

ISSN: (e) 3007-1607 (p) 3007-1593

95. Sohal, R.S. and R. Weindruch, *Oxidative stress, caloric restriction, and aging.* Science, 1996. **273**(5271): p. 59-63.
96. Partridge, L. and D. Gems, *Mechanisms of aging: public or private?* Nature Reviews Genetics, 2002. **3**(3): p. 165.
97. Roth, G.S., et al., *Aging in rhesus monkeys: relevance to human health interventions.* Science, 2004. **305**(5689): p. 1423-1426.
98. Speakman, J.R. and S.E. Mitchell, *Caloric restriction.* Molecular aspects of medicine, 2011. **32**(3): p. 159-221.
99. Watt, F.M., *Mammalian skin cell biology: at the interface between laboratory and clinic.* Science, 2014. **346**(6212): p. 937-940.
100. Fuchs, E., *Cell biology: More than skin deep.* J Cell Biol, 2015. **209**(5): p. 629-632.
101. Nedergaard, J. and B. Cannon, *How brown is brown fat? It depends where you look.* Nature medicine, 2013. **19**(5): p. 540.
102. Romanovsky, A.A., *Skin temperature: its role in thermoregulation.* Acta physiologica, 2014. **210**(3): p. 498-507.
103. McDonald, R.B. and J.J. Ramsey, *Honoring Clive McCay and 75 years of calorie restriction research.* The Journal of nutrition, 2010. **140**(7): p. 1205-1210.
104. Bruss, M.D., et al., *The effects of physiological adaptations to calorie restriction on global cell proliferation rates.* American Journal of Physiology-Endocrinology and Metabolism, 2011. **300**(4): p. E735-E745.
105. Müller-Röver, S., et al., *A comprehensive guide for the accurate classification of murine hair follicles in distinct hair cycle stages.* Journal of Investigative Dermatology, 2001. **117**(1): p. 3-15.
106. Driskell, R.R., et al., *Hair follicle dermal papilla cells at a glance.* J Cell Sci, 2011. **124**(8): p. 1179-1182.
107. Schlake, T. *Determination of hair structure and shape.* in *Seminars in cell & developmental biology*. 2007: Elsevier.
108. Hsu, Y.-C., L. Li, and E. Fuchs, *Emerging interactions between skin stem cells and their niches.* Nature medicine, 2014. **20**(8): p. 847.
109. Stafstrom, C.E., *An introduction to seizures and epilepsy*, in *Epilepsy and the Ketogenic Diet*. 2004, Springer. p. 3-29.
110. De Boer, H.M., M. Mula, and J.W. Sander, *The global burden and stigma of epilepsy.* Epilepsy & Behavior, 2008. **12**(4): p. 540-546.
111. Kwan, P. and M.J. Brodie, *Early identification of refractory epilepsy.* New England Journal of Medicine, 2000. **342**(5): p. 314-319.
112. Blog, R.L. and N. by Age, *CPE Monthly: The Ketogenic Diet for Epilepsy–Learn About the Diet, the Medical Conditions It's Used to Treat, and Its Mechanism of Action By Rebecca Randall, MS, RD, and Sue Groveman, MS, RD, LDN Today's Dietitian Vol. 18 No. 5 P. 46.*
113. Sharma, S., et al., *Use of the modified Atkins diet in infantile spasms refractory to first-line treatment.* Seizure, 2012. **21**(1): p. 45-48.
114. Kossoff, E.H., *Nonpharmacological approaches: diet and neurostimulation*, in *Handbook of clinical neurology*. 2013, Elsevier. p. 803-808.
115. Sampaio, L.P.d.B., *Ketogenic diet for epilepsy treatment.* Arquivos de neuro-psiquiatria, 2016. **74**(10): p. 842-848.
116. Kang, H.-C. and H.D. Kim, *Diet therapy in refractory pediatric epilepsy: increased efficacy and tolerability.* Epileptic disorders, 2006. **8**(4): p. 309-316.
117. Martin, K., et al., *Ketogenic diet and other dietary treatments for epilepsy.* Cochrane Database of Systematic Reviews, 2016(2).
118. Jain, S., *Management of epilepsy with ketogenic diet.* Indian J Psychosocial Sci, 2017. **7**: p. 15-20.
119. Rogovik, A.L. and R.D. Goldman, *Ketogenic diet for treatment of epilepsy.* Canadian Family Physician, 2010. **56**(6): p. 540-542.
120. Rho, J.M., *How does the ketogenic diet induce anti-seizure effects?* Neuroscience letters, 2017. **637**: p. 4-10.
121. Lima, P.A.d., L.P.d.B. Sampaio, and N.R.T. Damasceno, *Neurobiochemical*

Frontier in Medical & Health Research

ISSN: (e) 3007-1607 (p) 3007-1593

mechanisms of a ketogenic diet in refractory epilepsy. Clinics, 2014. **69**(10): p. 699-705.

122. McDaniel, S.S., et al., *The ketogenic diet inhibits the mammalian target of rapamycin (mTOR) pathway.* Epilepsia, 2011. **52**(3): p. e7-e11.
123. Bough, K.J. and J.M. Rho, *Anticonvulsant mechanisms of the ketogenic diet.* Epilepsia, 2007. **48**(1): p. 43-58.
124. Danial, N.N., et al., *How does the ketogenic diet work? Four potential mechanisms.* Journal of child neurology, 2013. **28**(8): p. 1027-1033.
125. Lutas, A. and G. Yellen, *The ketogenic diet: metabolic influences on brain excitability and epilepsy.* Trends in neurosciences, 2013. **36**(1): p. 32-40.
126. Maroon, J., et al., *Restricted calorie ketogenic diet for the treatment of glioblastoma multiforme.* Journal of child neurology, 2013. **28**(8): p. 1002-1008.
127. Ohgaki, H. and P. Kleihues, *Genetic alterations and signaling pathways in the evolution of gliomas.* Cancer science, 2009. **100**(12): p. 2235-2241.
128. Bloch, O., et al., *Impact of extent of resection for recurrent glioblastoma on overall survival.* Journal of neurosurgery, 2012. **117**(6): p. 1032-1038.
129. Anton, K., J.M. Baehring, and T. Mayer, *Glioblastoma multiforme: overview of current treatment and future perspectives.* Hematology/Oncology Clinics, 2012. **26**(4): p. 825-853.
130. Stupp, R., et al., *Effects of radiotherapy with concomitant and adjuvant temozolomide versus radiotherapy alone on survival in glioblastoma in a randomised phase III study: 5-year analysis of the EORTC-NCIC trial.* The lancet oncology, 2009. **10**(5): p. 459-466.
131. Mason, W., et al., *Canadian recommendations for the treatment of glioblastoma multiforme.* Current Oncology, 2007. **14**(3): p. 110.
132. Nebeling, L.C., et al., *Effects of a ketogenic diet on tumor metabolism and nutritional status in pediatric oncology patients: two case reports.* Journal of the American College of Nutrition, 1995. **14**(2): p. 202-208.
133. Zuccoli, G., et al., *Metabolic management of glioblastoma multiforme using standard therapy together with a restricted ketogenic diet: Case Report.* Nutrition & metabolism, 2010. **7**(1): p. 33.
134. Warburg, O., *On the origin of cancer cells.* Science, 1956. **123**(3191): p. 309-314.
135. Warburg, O., F. Wind, and E. Negelein, *The metabolism of tumors in the body.* The Journal of general physiology, 1927. **8**(6): p. 519.
136. Seyfried, T., et al., *The restricted ketogenic diet: An alternative treatment strategy for glioblastoma multiforme.* Treatment Strategies Oncology, London: Cambridge Research Centre, 2011: p. 24-35.
137. Seyfried, T.N., et al., *Metabolic management of brain cancer.* Biochimica et Biophysica Acta (BBA)-Bioenergetics, 2011. **1807**(6): p. 577-594.
138. Lee, C., et al., *Fasting cycles retard growth of tumors and sensitize a range of cancer cell types to chemotherapy.* Science translational medicine, 2012. **4**(124): p. 124ra27-124ra27.
139. Kossoff, E.H., et al., *Optimal clinical management of children receiving the ketogenic diet: recommendations of the International Ketogenic Diet Study Group.* Epilepsia, 2009. **50**(2): p. 304-317.
140. Freeman, J., et al., *The ketogenic diet: a treatment for epilepsy in children and others.* Demos, New York, 2006.
141. Mosek, A., et al., *Ketogenic diet treatment in adults with refractory epilepsy: a prospective pilot study.* Seizure, 2009. **18**(1): p. 30-33.
142. Weber, S., C. Mølgaard, and P. Uldall, *Modified Atkins diet to children and adolescents with medical intractable epilepsy.* Seizure, 2009. **18**(4): p. 237-240.
143. Marzetti, E., et al., *Cellular mechanisms of cardioprotection by calorie restriction: state of the science and future perspectives.* Clinics in geriatric medicine, 2009. **25**(4): p. 715-732.

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144. Hursting, S.D., et al., *Calorie restriction, aging, and cancer prevention: mechanisms of action and applicability to humans.* Annual review of medicine, 2003. **54**(1): p. 131-152.
145. Doyle, C., et al., *Nutrition and physical activity during and after cancer treatment: an American Cancer Society guide for informed choices.* CA: a cancer journal for clinicians, 2006. **56**(6): p. 323-353.
146. Moreschi, C., *Beziehung zwischen ernahrung und tumorwachstum.* Z Immunitatsforsch, 1909. **2**: p. 651-675.
147. Tannenbaum, A., *The dependence of tumor formation on the composition of the calorie-restricted diet as well as on the degree of restriction.* Cancer research, 1945. **5**(11): p. 616-625.
148. Hursting, S.D., S.N. Perkins, and J.M. Phang, *Calorie restriction delays spontaneous tumorigenesis in p53-knockout transgenic mice.* Proceedings of the National Academy of Sciences, 1994. **91**(15): p. 7036-7040.
149. Hursting, S.D., et al., *Diet and cancer prevention studies in p53-deficient mice.* The Journal of nutrition, 2001. **131**(11): p. 3092S-3094S.