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Theme

The use of ketogenic diet for treatments of diseases: A meta-analysis

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Abstract

The ketogenic diet is a low-carbohydrate and fat-rich diet. Its medicinal uses have been known since the early 1920's as a treatment for epilepsy where gave very encouraging results. Today there are many studies on the use of ketogenic diet to treat many diseases, whether it is added to pharmaceutical treatment or used alone. Recent work over the last decade or so has provided evidence of the therapeutic potential of ketogenic diets in many pathological conditions, such as diabetes, Alzheimer disease, Parkinson disease, cancer and coronavirus disease 2019. The goals of this review is to shed light on the effectiveness of ketogenic diet in treating or improving the treatment of these diseases, also, we take a closer look at the mechanism of action and the method of initiation the ketogenic diet. Moreover, we will learn about the types of ketogenic diet, as well as the use of ketogenic diet in sports and weight loss.

Keywords: ketogenic diet; epilepsy; cancer; diabetes; Alzheimer disease.

الملخص
النظام الغذائي الكيتوني هو نظام غذائي منخفض الكربوهيدرات وغني بالدهون. عُرفت استخداماته الطبية منذ أوائل العشرينات من القرن الماضي كعلاج للصرع حيث أعطى نتائج مشجعة للغاية. يوجد اليوم العديد من الدراسات حول استخدام النظام الغذائي الكيتوني في علاج العديد من الأمراض، سواء تمت إضافته إلى العلاج الدوائي أو استخدامه بمفرده. قدمت الأعمال الأخيرة على مدار العقد الماضي أو نحو ذلك دليلًا على الإمكانات العلاجية للنظام الغذائي الكيتوني في العديد من الحالات المرضية، مثل مرض السكري ومرض الزهايمر ومرض باركنسون والسرطان ومرض فيروس كورونا 2019. تهدف هذه المراجعة إلى إلقاء الضوء على فعالية النظام الغذائي الكيتوني في علاج أو تحسين علاج هذه الأمراض، كما أننا نلقي نظرة فاحصة على آلية العمل وطريقة بدء النظام الغذائي الكيتوني. علاوة على ذلك، سوف نتعرف على أنواع النظام الغذائي الكيتوني، وكذلك استخدام النظام الغذائي الكيتوني في الرياضة وفقدان الوزن.

الكلمات المفتاحية: النظام الغذائي الكيتوني؛ الصرع؛ سرطان؛ داء السكري؛ مرض الزهايمر.

Résumé

Le régime cétogène est un régime pauvre en glucides et riche en graisses. Ses usages médicinaux sont connus depuis le début des années 1920 comme traitement de l'épilepsie et ont donné des résultats très encourageants. Aujourd'hui, il existe de nombreuses études sur l'utilisation du régime cétogène pour traiter de nombreuses maladies, qu'il soit ajouté à un traitement pharmaceutique ou utilisé seul. Des travaux récents au cours de la dernière décennie environ ont fourni des preuves du potentiel thérapeutique des régimes cétogènes dans de nombreuses conditions pathologiques, telles que le diabète, la maladie d'Alzheimer, la maladie de Parkinson, le cancer et la maladie à coronavirus 2019. Les objectifs de cette revue sont de faire la lumière sur l'efficacité du régime cétogène dans le traitement ou l'amélioration du traitement de ces maladies, nous examinons également de plus près le mécanisme d'action et la méthode d'initiation du régime cétogène. De plus, nous en apprendrons davantage sur les types de régime cétogène, ainsi que sur l'utilisation du régime cétogène dans le sport et la perte de poids.

Mots clés : régime cétogène ; épilepsie ; cancer ; diabète ; maladie d'Alzheimer.

List of Common Abbreviations and Nomenclature

A1R : adenosine receptors

AA : arachidonic acid

ACA : acetoacetate

AcAc : acetoacetate

ACAT1 : Acetyl-Coenzyme A acetyltransferase 1

Acetyl- CoA : acetyl coenzyme A

AD : Alzheimer's disease

ADP : Adenosine diphosphate

AED : automated external defibrillator

AKT : Protein kinase B

ALS : amyotrophic lateral sclerosis

AMPA : α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid

AMPK : adenosine monophosphate-activated protein kinase

ApoE : apolipoprotein E

APP : amyloid precursor protein

AS : angelman syndrome

ASC : apoptosis-associated speck-like protein containing a caspase recruitmentdomain

ASD : Autism Spectrum Disorder

ATEC : Autism Treatment Evaluation Checklist

ATP : adenosine triphosphate

Aβ : amyloid β-peptide

BBB : blood brain barrier

BD : 3-butandeniol

BDH : beta-hydroxybutyrate dehydrogenase

BDH1 : D-beta-hydroxybutyrate dehydrogenase 1

BDNF : brain-derived neurotrophic factor

BHB : Beta-hydroxybutyrate

bOHB : b-hydroxybutyrate

C57BL6/J : model of labo mice

CA3 : Carbonic Anhydrase 3

CAT : carnitine-acylcarnitine translocase

CCL2/MCP-1 : monocyte chemoattractant protein 1

CHO : carbohydrate

CIM : carbohydrate-insulin model

CKD : Classical ketogenic diet

CNS : Central Nervous System

COVID-19 : Coronavirus disease 2019

COX1 : Cyclooxygenase 1

COX2 : Cyclooxygenase 2

CPT-1 : carnitine palmitoyl transferase 1

CR : Calorie restriction

CVD : Cardiovascular disease

DAMPs : damage-associated molecular patterns

DHA : docosahexanoic acid

DKA : diabetic ketoacidosis

DM : Diabetes mellitus

DS : Down syndrome

E4 : epsilon 4

EEG : electroencephalogram

EMCV : encephalomyocarditis virus

EPA : eicosapentanoic acid

FA : fatty acids

FAO : fatty acid oxidation

FFA : Elevated free fatty acids

GABA : Gamma-Amino Butyric Acid

GABAA : Gamma-Amino Butyric Acid-A

GAD : glutamic acid decarboxylase

GDNF : glial cell line-derived neurotrophic factor

GI : glycemic index

GL : glycemic load

GLUT1 : glucose transporter type 1

GPR109A : G-protein-coupled receptor

GWAS : genome-wide association studies

HCA2 : hydroxy-carboxylic acid receptor 2

HCV : hepatitis C virus

HDACs : histone deacetylases

HDL : high-density lipoproteins

HFD : high fat diet

HR_{max} : Maximum Heart Rate

IAV : influenza A virus

IGF : insulin-like growth factor

IGF-1 : Insulin-like growth factor 1

IL-1β : Interleukin 1 beta

ILAE : International League Against Epilepsy

K2P : Two-pore domain K+ channels

KATP : ATP-sensitive potassium

Kb : Ketone bodies

KD : ketogenic diets

KDT : ketogenic diet therapy

KE : ketone esters

KS : ketone salts

LC : low-carbohydrate

LCD : low carbohydrate diets

LDL : low-density lipoprotein

LGID : The low glycemic index diet

LKB1 : Liver kinase B1

LPS : lipopolysaccharide

M1 : macrophage type 1

M2 : macrophage type 2

MAVS : mitochondrial antiviral signaling

MCT : medium-chain triglyceride

MCT : monocarboxylic acid transporter

MCT-1 : monocarboxylate transporter-1

MERS-CoV : Middle East respiratory syndrome coronavirus

mKATP : The mitochondrial ATP-sensitive potassium channel

MKD : Modified ketogenic diet

mPT : mitochondrial permeability transition

MPTP : 1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine

MRC : mitochondrial respiratory complexe

mTOR : The mechanistic target of rapamycin

NADH : nicotinamide adenine dinucleotide (NAD) + hydrogen (H)

NF-KB : Nuclear factor-κB

NFTs : neurofibrillary tangles

NLR : (Nod)-like receptor

NLRP3 : NLR family pyrin domain containing 3

NMDA : N-methyl-D-aspartate

NO : Nitric oxide

NRF2 : nuclear factor erythroid 2–related factor 2

NT-3 : neurotrophin-3

ob/ob : model of labo mice

OXPHOS : Oxidative phosphorylation

PAMPs : pathogenassociated molecular patterns

PCr:Cr : phosphocreatine:creatine

PD : Parkinson's disease

PDH : pyruvate dehydrogenase

PGC1α : proliferator-activated receptor gamma coactivator 1-alpha

PGD2 : Prostaglandin D2

pH : potential of hydrogen

PI3K : Phosphoinositide 3-kinases

PIGD : postural-instability-gait-disorder

PMD: Pelizaeus-Merzbacher disease

PPARα : peroxisome proliferator-activated receptor-α

PPARγ : peroxisome proliferator-activated receptor γ

PRRs : pattern recognition receptors

PUFA : polyunsaturated acid

RNA : ribonucleic acid

ROS : reactive oxygen species

SARS-CoV : Severe acute respiratory syndrome coronavirus

SARS-CoV 2 : Severe acute respiratory syndrome coronavirus 2

SCOT : Succinyl-CoA:3-ketoacid CoA transferase

SD : standard a chow diet

SIRT1 : sirtuin 1

T1D : type 1 diabetes

TCA : tricarboxcylic acid

TCA cycle : tricaboxylic acid cycle

TCR : Tcell receptors

TNF-α : tumor necrosis factor alpha

Treg : regulatory T cells

TrkB : Tropomyosin receptor kinase B

UCP : uncoupling protein

UPDRS : Unified Parkinson's Disease Rating Scale

VGLUT : The vesicular glutamate transporter

VLCKD : very low-carbohydrate ketogenic diets

$VO2_{max}$: maximal oxygen uptake

βOHB : β-hydroxybutyrate

γδ T cells : Gamma delta T cells

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Introduction

Introduction

In the last decades, low carbohydrate diets (LCD) and ketogenic diets (KD) have become widely known and popular ways to lose weight, not only within the scientific community, but also among the general public, with best-selling dedicated books or intense discussion on social media networks staying at the top of the diet trend list for years. These dietary approaches are effective for losing weight, but there is growing evidence suggesting that caution is needed, especially when these diets are followed for long periods of time, or by individuals of a very young age or with certain diseases (Ioannidis, 2018; American Diabetes Association, 2019).

The ketogenic diet (KD), developed in the early1920s, had fallen into disuse during the 1970s and1980s with the rapid development of new anticonvulsant agents for epilepsy (Swink *et al*., 1997). The recent resurgence of interest and use of the diet can be dated to the American Epilepsy Society's meeting in 1996. Currently, it is perhaps more effective than most of the newer medications. The rediscovery of this effective therapy for childhood epilepsy has, within the past decade, had a major impaction the most difficult to control seizures of childhood and promises to have an impact on adults with epilepsy as well. It will, perhaps, be used for other medical conditions as well. New research into its mechanism of action shows promise in changing our thinking about cerebral metabolism and our understanding of the control of epilepsy (John *et al*., 2006).

In this context, the objectives of our study are highlighting the medical utilization of the ketogenic diet on treatment of diseases and the extent of its effectiveness also the method of initiation the diet and the duration of its use.

For this purpose, we divided our work into three parts:

- The first part present an overview on the ketogenic diet
- The second part highlight the method of initiation of the ketogenic diet
- The third part we studied the medicals uses of ketogenic diet for the treatment of: epilepsy; covid-19; Alzheimer disease; Parkinson disease; type 2 diabetes and cancer.

Chapter I

General information on the ketogenic diet

Chapter I: General information on the ketogenic diet

I.1 Definition

The term 'ketogenic diet' was first used by Russel Wilder in 1923 to describe a high-fat, low-carbohydrate diet that produced ketonemia. He used it as an alternative to fasting (then in vogue as a therapeutic option) for the management of epilepsy (Wheless, 2008). In the most general terms, a ketogenic diet is any diet that causes ketone bodies to be produced by the liver, shifting the body's metabolism away from glucose and towards fat utilization. More specifically, a ketogenic diet is one that restricts carbohydrates below a certain level (generally 100 grams per day), inducing a series of adaptations to take place. Protein and fat intake are variable, depending on the goal of the dieter. However, the ultimate determinant of whether a diet is ketogenic or not is the presence (or absence) of carbohydrates (Lyle McDonald, 1998).

The KD drastically limits carbohydrate intake, replacing lost calories with fat, while maintaining a normal protein intake. It consists of around 80% fat, 15% protein, and 5% carbohydrates (Rogovik and Goldman, 2010; Freeman *et al*., 2000). Traditional KD involves the use of lipid:nonlipid ratios measured in grams (g) (Rogovik and Goldman, 2010). Today, the KD's goal lipid:nonlipid ratio ranges from 4:1 to 2:1, with the higher ratio being more effective (Rogovik and Goldman, 2010; Seo *et al*., 2007).

I.2 History

High fat diets were considered nearly 140 years ago, but the first American use of the diet appears to have been near the beginning of the last century when a faith healer (Bernarr Macfadden) and an osteopathic physician (Dr. Hugh Conklin) advocated the use of fasting and prayer in a boy with seizures (Swink *et al*., 1997). As metabolism was better understood, the concept evolved that a high-fat diet could mimic the ketosis found during fasting. Around the same time, Wilder introduced the concept of a diet consisting of "ketogenic" and "antiketogenic" components for the treatment of epilepsy (Wilder, 1921; Swink *et al*., 1997). Groups in Minnesota, New York, and Maryland studied and used the diet in the intervening years, but its use appears to have declined with the introduction of diphenylhydantoin (phenytoin) in 1938 (Houston Merritt and Putnam, 1938). About 12 years ago, the treatment of a child at the Johns Hopkins Hospital precipitated the most recent interest in the ketogenic diet (Freeman *et al*., 2006a).

Ten years ago, the KD was nearly unknown internationally. In the past 8 years, there has been a dramatic increase in its use worldwide, and currently75 centers in45 countries offer the KD (Kossoff and McGrogan, 2005). With the exception of parts of Central America and Africa, parents only need look to their country or a neighbor for a KD center. There have been sponsored conferences and symposia in Canada, Croatia, Cuba, England, Germany, Greece, India, and Italy in the past 2 years alone.

Cultural, religious, and financial differences among these centers have led to differences in approaches to providing the KD. Some use less or no fasting, some use different ratios (to encompass more rice and less fat in some countries in the East), and some allow increased fluid and calorie consumption (Kossoff and McGrogan, 2005).

I.3 Types of ketogenic diet and compositions

Various forms of KD are now used in clinical practice. The amount of carbohydrates permitted varies from 20 to 50 g/day. This depends upon personal metabolic and weight loss goals, upon the planned duration of KD, and upon individual health status, Table 1 shows the types of keto and the characteristics of each type. The classic therapeutic KD, initially created for the management of childhood seizures, has a 4:1 ratio of fats to combined protein and carbohydrates. A medium-chain triglyceride (MCT) variant (the MCT KD) utilized to more ketogenic MCT (present in coconut oil) to provide half of all consumed calories. The Atkins diet—popular in lay literature—and the low glycemic index diet are less restrictive variants of KD. Fluid restriction is not advocated in modern KD, due to the risk of constipation and nephrolithiasis. Vegetarian and vegan KD are also available (Hartman and Vining, 2007).

Table1: Characteristics of ketogenic diets (Kossoff and Hartman, 2012).

Macronutrients	**Classical Ketogenic Diet**	**MCT-Based Diet**	**Modified Atkins Diet**
	Energy (%)		
Fat	90	70	70
Protein	7	10	25
Carbohydrates	8	20	5

I.3.1 Classical ketogenic diet (CKD)

The traditional "classic" ketogenic diet contains a fixed ratio by weight of fat to combined protein and carbohydrate (table 1).This diet is characterized by a high fat content, few carbohydrates, and normal protein content, Table 2 shows the components, advantages and disadvantages of KD. Whereas carbohydrates constitute approximately 55% of the energy value in the traditional diet, with approximately 30% of fat and 15% of protein, these proportions in classical KD are up to 8% for carbohydrates, 90% for fat, and approximately 7% for protein (Li´skiewicz *et al*., 2012; Kossoff and Hartman, 2012). This is achieved by excluding high-carbohydrate foods while increasing the consumption of foods high in fat. In young children and infants, the traditional diet is frequently started in a hospital setting (Radhika Dhamija, 2013).

I.3.2 Modified ketogenic diet (MKD)

Modified Atkins diet allows for carbohydrate intake of 10-20g/day and strongly encourages fat intake (table 1). There is no calorie restriction or meticulous weighing of food involved and hence meals are easier to prepare (table 2). It can be started in home setting. This diet appears to be well-tolerated and efficacious in most children (Kossoff *et al*., 2006). Long-term experience with this diet has also been reported in 87 children with intractable epilepsy, of which 54 continued for more than six months. After a mean of 19.9 months, 30 of 54 (55%) children with diet durations of more than six months achieved >50% improvement; 19 (35%) were seizure-free. At 12 months, 33 of 87 (38%) had >50% seizure reduction; 16 (18%) were seizure-free (Chen and Kossoff, 2012).

I.3.3 Medium chain triglyceride (MCT) diet

Most dietary fat is made of molecules called long-chain triglycerides. However, medium-chain triglycerides (MCTs) of octanoic and decanoic acids produce more ketones per unit of energy (Huttenlocher *et al*., 1971; Freund and Weinsier, 1966). A variant of the classic diet known as the MCT ketogenic diet uses MCT oil to provide around half the calories. As less overall fat is needed in this diet, a greater proportion of carbohydrate and protein can be consumed, allowing a slightly greater variety of food choices (table 2). Dr. Huttenlocher first tested this diet in 1971 on twelve children and adolescents with intractable seizures. A therapeutically significant anticonvulsant effect was seen in 50% of the children with a mean age of eight years with slightly higher incidence of gastrointestinal side effects (Huttenlocher

et al., 1971). In another study on children with refractory epilepsy > 50 % of patients had > 75 % reduction in seizure frequency using MCT diet (Mak *et al*., 1999).

I.3.4 The low glycemic index diet (LGID)

The low glycemic index treatment is a low-carbohydrate diet (carbohydrate intake is usually limited to 40-60g/day). Only foods with low glycemic index (< 50) are used (table 2). In a study on 20 patients who had failed at least three anticonvulsant medications previously, 50% had greater than 90% reduction in the seizures (Pfeifer HH and Thiele EA, 2005). In another retrospective chart review study, 40 % of the enrolled patients with generalized or focal seizures, refractory to at least three consecutive anticonvulsant drugs, with at least four seizures per month, had a 75-90% seizure reduction (Coppola G *et al*., 2011).

Table2: Composition and pros/cons of the different ketogenic diets (Radhika Dhamija, 2013).

Diet	Composition	Pros	Cons
Classical KD	Can be any ratio but typically 3-4:1 Based on 4:1 ratio: 90% fat, 4% carbohydrate, 6% protein	Parents know exactly how much of each food to give; Very consistent, therefore little variation in ketones; Easy to adjust as dietician knows exactly what child is getting; Requires less record keeping by parents	Difficult to adjust amount consumed based on child's appetite; Child must eat everything on their plate; Protein limited to recommended dietary allowance, which is often less than child is used to; Involves weighing and measuring; more time-consuming to prepare the meals
Medium Chain Triglyceride	Can be any ratio Based on 4:1 ratio: 10% LCT fat, 60% MCT fat, 20% carbohydrate, 10% protein	Provides more protein; Greater protein serving size allows more volume in which to mix the fats and increased variety of food;	Involves weighing and measuring food; time-consuming to prepare the meals; Gastrointestinal side effects
Modified Atkins	Approx 1.1:1 ratio 65% fat, 10% carbohydrate, 25% protein	Greater flexibility to adjust meal to variations in appetite; Provides more protein; Greater protein serving size allows more volume in which to mix the fats; Less weighing, measuring, faster meal prep;	No firm guidelines regarding fat amounts; Requires experimentation to determine adequate fats to ensure desired ketosis; Often more variability in ketone production; Requires more record keeping to allow adjustments in diet
Low glycemic index diet	Approx 0.6:1 ratio 60% fat, 10% carbohydrate, 30% protein	Greater flexibility to adjust meal to variations in appetite; Provides more protein; Greater protein serving size allows more volume in which to mix the fats; Less weighing, measuring, faster meal prep;	Requires knowledge of the foods that have low glycemic index; Requires more record keeping to allow adjustments in diet

I.4 Biochemistry behind the KD

The KD's objective is to create a state of ketosis. Ketosis is ketone generation and accumulation as a result of excessive breakdown of fat because of inadequate carbohydrate use (Mosby's Medical Dictionary, 2009). Essentially, the body shifts from using glucose as its main source of fuel to using ketone bodies (KB) (Figure 1), one must understand some basics:

• The body relies on glucose for adenosine triphosphate (ATP) production in a normal diet.

• In starvation conditions, the body resorts to using its fat stores by fatty-acid oxidation. Fatty-acid oxidation generates KBs that are used as an alternate fuel source for ATP production.

• By reducing carbohydrate intake, the KD mimics this "starvation mode." This change in metabolic function causes a variety of downstream effects, such as increased mitochondrial efficiency and reduced production of reactive oxygen species (ROS).

After several days of following the KD, the carbohydrate-starved body depletes its glucose stores (Paoli, 2014). With an abundance of fatty acids and scarcity of carbohydrates, the body shifts to fatty-acid oxidation as its primary method of energy generation. Unlike glucose, fatty acids cannot be transported through the blood brain barrier (BBB) (Paoli, 2014; Hartman *et al*., 2007). The body must resort to other metabolic mechanisms to break down the fatty acids into components that can be transported through the BBB. To maintain normal blood glucose levels:

• The liver diverts oxaloacetate from normal energy production in the Krebs cycle (a sequence of chemical reactions that convert glucose, proteins, and fats into energy) to the process of gluconeogenesis (Hartman *et al*., 2007). Diverting oxaloacetate cripples the Krebs cycle, reduces its efficiency, and prevents processing of the extra acetyl-CoA.

• Fatty-acid oxidation generates high quantities of acetyl-CoA that would normally be processed by the hepatic Krebs cycle (Hartman *et al*., 2007).

• The hepatic mitochondrial matrix converts the excess acetyl-CoA units to acetoacetate.

• Acetoacetate is spontaneously decarboxylated into acetone and is also enzymatically converted to beta-hydroxybutyrate (Paoli, 2014; Hartman *et al*., 2007). Acetoacetate, acetone, and beta-hydroxybutyrate are all KBs that can pass through the BBB and are alternative fuel sources for the brain and other tissues. KB formation is referred to as ketogenesis, giving the KD its name. Centrally, the brain's mitochondria take up the KBs and use multiple enzymes to convert them back into acetyl -CoA. ATP production follows (Hartman *et al*., 2007).

A similar process occurs in other extrahepatic tissues' mitochondria. Ketogenesis increases blood and urine KB levels. One method to check whether ketosis is occurring involves the use of a urine dipstick that can detect the presence of ketone bodies. Most urine dipstick tests report a value of 0 to 4+, which correlates to a ketone concentration of 0 to > 16 mmol/L (van Delft *et al*., 2007). Diabetics often use dipsticks to monitor for a related but clinically different condition known as diabetic ketoacidosis (DKA).

In DKA, KBs and associated protons are produced very rapidly, overwhelming the body's acid-base buffering system (Manninen, 2004). DKA is a life-threatening medical emergency and must be treated. Dietary ketosis is a much more gradual process, thus safer. KB blood levels reach a maximum level of 7 to 8 mmol/L with minor alterations in pH, whereas in DKA the levels can reach 20 mmol/L and cause an acidic pH (Paoli, 2014). Patients with ketosis subsequent to the KD or undiagnosed diabetes share another clinical feature: sweet breath odor. This is the result of acetone's volatility and respiration from the lungs (Paoli, 2014).

Dieters use KBs as their main fuel source, but blood sugar levels remain physiologically normal, though on the lower end of the spectrum (Paoli, 2014; Paoli *et al*., 2013). This physiologically normal blood-glucose level originates from glucose production from glucogenic proteins and the liberation of glycerol during fatty-acid oxidation (Paoli, 2014; Paoli *et al*., 2013). Through this process, cells that strictly require glucose, such as red blood cells (that lack mitochondria), are able to meet their metabolic demand (Manninen, 2004).

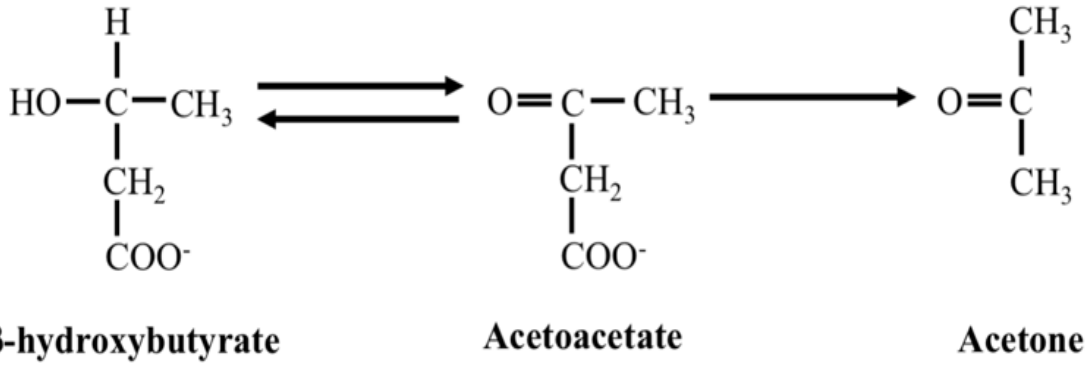

Figure 1 : Structure of ketone bodies.

I.5 Ketogenic diets and weight Loss

The prevalence of obesity in the United States remains a significant public health issue, as nearly one-third of men and women are classified as overweight or obese (Bhupathiraju, 2016. This increase in body weight and adipose tissue mass increases the risk of developing hypertension (Ryu *et al*., 2019), type II diabetes (American Diabetes Association, 2016), and CVD (Ortega *et al*., 2016) . Behavioral modifications, specifically dietary strategies and physical activity/exercise, are recommended to combat obesity. Over the years, numerous "fad diets," such as the Atkins or South Beach diets, have been popularized for weight loss with varying levels of patient outcomes, scientific evidence, and support from the medical community (Kuchkuntla *et al*., 2018). More recently, the KD has been proposed as a strategy for combatting obesity, since it induces rapid weight loss. The lack of carbohydrate availability in the diet is proposed to induce fatty acid mobilization from adipose tissue as a way to supply energy to the body via ketone bodies, resulting in an efficient method of promoting weight loss (Paoli, 2014).

Although the precise composition of the KD varies throughout the literature, the diet is typically defined as a low carbohydrate diet that contains adequate protein (15–20%) and high caloric intake from fat. The original KD was developed by physician-researchers, Woodyatt and Wilder, at the Mayo Clinic in the early 1920s, as a treatment for diabetics and epileptic children (Wilder, 1921; Woodyatt, 1921). The dietary regimen called for 1 gram per kg of body weight of protein, 10–15 grams of carbohydrates per day, and the balance of the intake in the form of fats, resulting in an approximate fat to protein plus carbohydrate ratio of 4:1. That dietary composition is the classical Peterman KD, named after the physician who reported the formulation (Peterman, 1925). The KD was a frequent treatment for epilepsy in children until the introduction of antiepileptic drugs in the late 1930s, but remained prominent in medical textbooks until the 1980s (Wheless, 2008). The KD reemerged in the late 1990s as a treatment for intractable epilepsy or refractory seizures (Wheless, 2008), and remains a viable therapy in instances where pharmacological intervention is not sucient. In the last 20 years, the KD has been effective in the treatment of patients with inherited metabolic disorders, such as glucose transporter type 1 (GLUT1) deficiency, pyruvate dehydrogenase deficiency, and glycogen storage diseases (Scholl-Burgi *et al*., 2015).

Over the last decade, research on the effectiveness of the KD in a variety of diseases and conditions has increased significantly. Human studies typically use low-carbohydrate (LC),

which is not necessarily a true KD, or very low-carbohydrate ketogenic diets (VLCKD), in which carbohydrate intake can range between 20–50 grams per day or less than 10% of calories, respectively (Shai *et al*., 2008; Sondike *et al*., 2003). In some studies, the term Atkins diet is also used (Dansinger *et al*., 2005; McAuley *et al*., 2005). In other studies, the LC diets are more aligned with reduced carbohydrate diets (intakes of 35–45% calories per day) (De Souza *et al*., 2012; Sacks *et al*., 2009). Thus, the precise characteristics of the dietary intervention are important in the ultimate interpretation of the results (Kristin *et al*., 2019).

Several human studies evaluated the benefits of LC or KD diets on weight loss. In a one-year study of 160 overweight and obese individuals, the Atkins diet lowered body weight, cholesterol, and insulin to the same degree as low-fat, caloric restriction, or reduced carbohydrate (40% of calories) diets (Dansinger *et al*., 2005). A similar observation was made in 90 patients with increased risks of CVD and type 2 diabetes after 6 months of dietary intervention (McAuley *et al*., 2005). A 12-week LC diet in adolescents led to significant reductions in body weight and LDL cholesterol compared to a low-fat diet (Sondike *et al*., 2003). Conversely, LC diets showed similar weight loss compared to low-fat diets in obese patients after 2 years (Shai *et al*., 2008; Foster *et al*., 2010). However, the LC diet was met with an improvement in blood lipid profiles and other CVD risk factors (Shai *et al*., 2008; Foster *et al*., 2010). A reduced carbohydrate diet (35–45% caloric intake) showed similar weight loss compared to a reduced fat diet (20% calories) in approximately 400 and 800 overweight adults after 2 years of treatment (De Souza *et al*., 2012; Sacks *et al*., 2009). In a meta-analysis study encompassing ~1600 patients, a VLCKD diet achieved greater weight loss, reduced diastolic blood pressure, lowered serum triglyceride levels, and elevated HDL levels compared to a low-fat diet at 12 and 24 months (Bueno *et al*., 2013). Unfortunately, LDL levels were significantly higher in the VLCKD patients (Bueno *et al*., 2013). In total, a reduction and restriction of carbohydrate intake appears to be sucient to promote weight loss. However, whether this dietary strategy is more effective than other methods is not clear. It should be noted that the above studies did not evaluate serum ketone body levels, so whether the weight loss is associated with ketosis or a ketogenic effect is not known (Kristin *et al*., 2019).

In the aforementioned human studies, a major limitation is patient adherence to the assigned dietary intervention. Therefore, animal studies, particularly in rodent models, may provide better insight. Some studies in mice utilize diets that are more reflective of a true KD, in which fat represents 90–95% of the total calories, protein 5–10%, and carbohydrates ~1% (Wentz *et al*., 2010; Kennedy *et al*., 2007; Badman *et al*., 2009; Ellenbroek *et al*., 2014). When

C57BL6/J mice are fed a KD for 5 to 8 weeks, mild weight loss (~10%) occurs, particularly in the first 1–3 weeks (Wentz *et al*., 2010; Kennedy *et al*., 2007). In addition, KD-fed mice gain significantly less weight than mice fed a high fat diet (HFD, 60% of total calories) (Kennedy *et al*., 2007). Although a 5-week treatment of KD in mice being fed a HFD for 12 weeks reduces body weight (Kennedy *et al*., 2007), KDs in ob/ob mice are not effective at reducing obesity (Badman *et al*., 2009). Moreover, long-term treatment (22 weeks) of mice with KD does not result in body weight changes and may lead to glucose intolerance and insulin resistance (Ellenbroek *et al*., 2014). These studies support the KD as a weight loss strategy in mice, particularly in the short-term. However, long-term consumption of the KD, especially with an extremely high fat content and reduced protein, may result in unexpected consequences (Kristin *et al*., 2019).

I.6 Ketogenic diet and sports

Even though there are still many concerns about the use of KD in sports (Franchini *et al*., 2012), some encouraging findings on KD and performance (Paoli *et al*., 2012; Zajac *et al*., 2014) underline the need for an in-depth understanding of its mechanisms of action for sports purposes (Figure 2). Based on previous research on KD in weight loss, neurological diseases, and, in general, on health-related conditions, we can propose some interesting fields of action of KD in sports. It is a type of diet that appears to have several advantages over other types of extreme energy-restricted ‘‘crash’’ diets V the latter, even if used for just a few days, can create situations of undernutrition for essential nutrients (vitamins, minerals, essential fatty acids, and amino acids) as well as depriving the body of other macronutrients that help control oxidative stress and inflammatory processes. An energy-sufficient KD diet with an adequate amount of protein (minimum 1,3-1,5 g kg-1 of body weight) is not an ‘‘extreme’’ diet apart from the very low carbohydrate levels (G20 g carbohydrates d-1) and, as such, it does not lead to metabolic imbalances that can have irreversible effects if nutrient-deficient weight loss diets are repeated on a regular basis (Paoli *et al*., 2015b).

I.6.1 Ketogenic diet and muscle mass

Unlike severe energy restriction, KD provides adequate amounts of energy and protein to athletes (Paoli *et al*., 2012), avoiding protein deficiency but, at the same time, the KD, by inducing a ‘‘fasting-like’’ state, leads to alterations in metabolic pathways and processes such as autophagy and stress resistance. KD ‘‘mimics’’ energy restriction effects on 5 adenosine monophosphate-activated protein kinase (AMPK), sirtuin-1 (SIRT-1), and peroxisome

proliferator-activated receptor gamma coactivator 1-alpha (PGC1α), which become activated by phosphorylation (Longo and Mattson, 2014). In this state, PGC1α moves to the nucleus and acts as a transcription factor, increasing the expression of genes that code for proteins involved in fatty acid transport, fat oxidation, and oxidative phosphorylation. The activation by phosphorylation of PGC1α may occur in several ways involving AMPK, calcium calmodulin-dependent protein kinase, and p38 mitogen-activated protein kinase pathways. SIRT-1 mediated deacetylation also can cause activation. AMPK1 can work in two ways, either by activating PGC1α by phosphorylation or else directly by promoting the expression of enzymes involved in skeletal muscle oxidative effects and metabolism. This is supported by observations that, in obese subjects, the skeletal muscle is less oxidative and has, during fasting, lower AMPK activation (Draznin *et al*., 2012). At the same time, AMPK activation also inhibits mammalian target of rapamycin (mTOR) signaling, which is an important factor involved in regulating muscle mass (Sandri *et al*., 2013).

Macronutrient intake can have an influence on these pathways. It has been shown that reducing carbohydrate intake to very low levels can lead to the activation of AMPK and SIRT-1, increased AMPK1 phosphorylation, and increased skeletal muscle PGC1α deacetylation but without affecting overall amounts of AMPK, PGC1α, or SIRT-1. The activations appear to occur in mice within just a few hours (~5 h) of initiation of starvation, currently though similar data are lacking in humans during KD. SIRT-1 and AMPK, when they are activated, can have beneficial effects on glucose homeostasis and insulin action (Draznin *et al*., 2012).

All these effects are positive in terms of health outcomes, but there is always the other side of the coin: KD, similar to fasting, blunts the insulin-like growth factor 1 (IGF-1)/AKT/ mTOR pathway, reducing the possibility of gaining muscle mass despite energy sufficiency (Sandri *et al*., 2013).

I.6.2 Ketogenic diet and strength

The effects of brief periods of KD on strength and power performance deserve close attention. As previously mentioned, for athletes competing in weight category sports, a safe method of weight loss that does not impair performance can be a legitimate and important tool. Surprisingly, there is only one study, performed by our own group, which has reported on this topic. We have demonstrated recently that, compared with a standard ad libitum diet, a 30-d KD did not affect explosive and strength performance negatively in a group of high-level gymnasts (Paoli *et al*., 2012). It should be underlined that, because of the intense physical

activity of competitive athletes, there is an increased demand for protein, and this was reflected in the KD administered in the study, which provided approximately 2.8 g protein kg-1 d-1(Paoli *et al*., 2012).

This is a fundamental point: an insufficient protein intake would be likely to negatively affect performance. Even with this amount of protein though, the athletes showed a decrease in body fat and a maintenance of muscle mass as a result of the well-documented ‘‘muscle-sparing effect,’’ which occurs after a few days of ketosis (Paoli *et al*., 2015b).

I.6.3 Ketogenic diet and endurance

The available data on the use of the KD in untrained/sedentary subjects have shown contradictory results, with some reports of improvement (Wycherley *et al*., 2014) and others of reduction (White *et al*., 2014) in physical performance. For example, in mildly obese untrained individuals, Phinney et al. noted that, while undergoing prolonged exercise at a level of 60% $VO2_{max}$, they can sustain this even with almost no carbohydrate in the diet (G10 g d-1) across a period of 6 wk. Furthermore, after a mean weight loss of 7.1 kg, there was a significant and surprising 155% increase compared with baseline in treadmill duration time (from 168 to 259 min) (Phinney *et al*., 1980). It has been reported by White and colleagues (White *et al*., 2014) that a KD (5% of energy provided by carbohydrates) increased perception of fatigue during a 9-min walk; however, it was only the rate of perceived exertion that was significantly higher , there was no actual change in average heart rate or exercise intensity (% HR_{max}), whereas other measures of performance such as $VO2_{max}$ and blood lactate levels were not analyzed. A couple of recent studies demonstrated instead that, in obese subjects, 8 wk of KD enhanced fat oxidation and had no detrimental effect on maximal or submaximal markers of aerobic exercise performance or muscle strength compared with a high-carbohydrate diet (Brinkworth *et al*., 2009). It also was reported that a KD can improve cognitive functioning slightly with respect to speed of processing (Halyburton *et al*., 2007). The authors suggest that a relatively long-term low-carbohydrate diet does not affect the ability to perform endurance or resistance exercises adversely. However, endurance athletes and sedentary subjects are somewhat different, and only very few studies have analyzed the effect of KD in the former. The earliest is the study by Phinney et al. (Phinney *et al*., 1983), which looked at the effect of chronic ketosis on performance in endurance athletes. They reported that 4 wk of ketogenic nutrition did not have any negative effects on the aerobic performance of endurance cyclists (Paoli *et al*., 2015b).

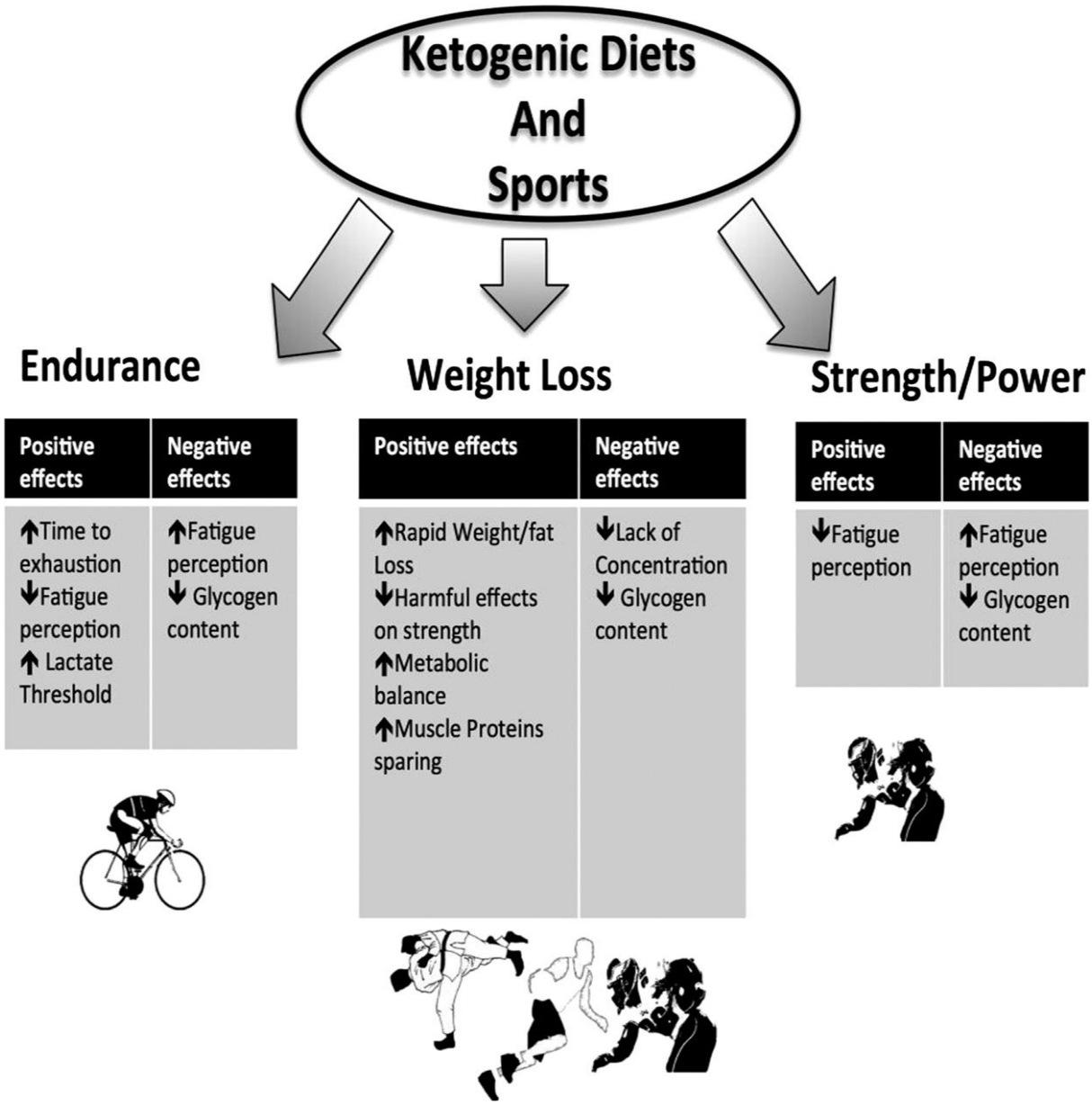

Figure 2: Effects of ketogenic diets in different sports variables and their plausible physiological mechanism (Paoli *et al*., 2015b).

Chapter II

Ketogenic diet initiation

Chapter II: Ketogenic diet initiation

II.1 Patient selection

Before staring the KD, parental education about the nature of the diet, side effects and benefits is very important. One must ensure that the family is committed to a trial of the diet and have resources available. Meeting a dietician prior to staring the diet is essential. All prescription medications should be changed to carbohydrate free or lowest carbohydrate content forms. Information about over the counter products that have low or no carbohydrates is also provided to families. Patients and families should understand that once started, this diet has to be followed closely otherwise its beneficial effect is lost (Livingston, 1951). There are two specific metabolic conditions in which the KD has unique efficacy, glucose transporter-1 deficiency and pyruvate dehydrogenase deficiency. In these disorders, the ketogenic diet should be initiated at the time of diagnosis (Kossoff *et al*., 2009).

KDTs can effectively treat epilepsy in individuals from infancy through adulthood. For years, it was thought that infants had difficulty maintaining ketosis while meeting their growth requirements. As a result, KDTs were not recommended for children younger than 2 years of age. A recent case report illustrates that KDTs are safe and effective for infants as young as 6 weeks (Thompson *et al*., 2009). In fact, there is now preliminary evidence that children younger than age 2 years may be an ideal age population in which to start the KD (Dressler A *et al*., 2015; Kim *et al*., 2016). Specific guidelines for prescribing KDTs to infants have been created in Europe (Louw *et al*., 2016).

The diet is no more restrictive for this age range than for younger children and has similar efficacy. Although it is apparent that adolescents experience a much more diverse set of life issues that could negatively affect the diet, equally strong motivation factors are present. In an era of new AEDs and vagal nerve stimulation, the ketogenic diet should be considered an option for the adolescent population (Mackenzie *et al*., 2003).

Evidence for KD use is less robust in adults (Mosek *et al*., 2009) and its use in adults less frequent among practicing physicians. Only 38% of the consensus group offered dietary therapy to adults (Kossoff *et al*., 2009). New diet options that are more palatable and flexible than the traditional KD, such as the modified Atkins diet or low glycemic index diet have made this an attractive option for adults with intractable epilepsy. In a prospective open-label pilot study on KD treatment in adults with refractory epilepsy (generalized and focal), 50% of subjects had a >50% reduction in seizures and 33% had a >85% seizure reduction. The diet was felt to be well

tolerated and adverse effects were mild: nausea, vomiting, diarrhea, constipation, and weight loss (Klein *et al*., 2010). A prospective, open-label study performed on 30 adults (>18 years-of-age, with at least weekly seizures, prior use of at least two anticonvulsants) using a modified Atkins diet showed that 47% had a >50% seizure reduction after one and three months on the diet; 33% after six months (Kossoff *et al*., 2008).

II.2 Initiation of dietary therapies

Most (20/25, 80%) centers begin the classic KD in the hospital so that the child can be observed closely, and medical interventions can be instituted if needed, Table 1 shows the Typical ketogenic diet initiation regimen. The hospital admission also provides more time for teaching of caretakers on how to calculate and weigh foods, monitor ketosis, and manage the KD once the patient leaves the hospital. It is not clear how frequently inpatient initiation unmasks rare metabolic disorders, since the advent of preadmission metabolic testing (Kossoff *et al*., 2018).

The KD can alternatively be started as an outpatient, based on several retrospective studies in which no fasting period was used (Vaisleib *et al*., 2004; Wirrell *et al*., 2002; Nathan *et al*., 2009). The potential advantages of this include reduced family stress, time away from home, and hospital-associated costs. Although, as stated previously, most centers still routinely admit for KD initiation, 23/25 (92%) believed that an outpatient initiation could be used in select situations. This percentage was higher than the 2009 consensus survey (73%). To initiate the classic KD as an outpatient, all children must be screened with metabolic testing, the child must be in proximity to medical care, and the KD team must be able to provide family education in an outpatient setting. A recent European consensus-based guideline recommends hospitalizing infants (<12 months) for initiation of the classic KD, using a nonfasting protocol (Louw *et al*., 2016).

The traditional method of initiating the KD involves a period of fasting (12–24 h), with no carbohydrate-containing fluids provided. For the first 24–48 h, serum glucose is monitored periodically (eg, before meals) and juice or other forms of dextrose are provided for values <30 mg/dl. The meals are then typically advanced daily to by one-third or one-half caloric intervals until full calorie meals are tolerated, while keeping the KD ratio constant, Table 2 shows the Nutritional Breakdown for Day 1. A different approach begins with full calories, but the KD ratio increases daily from 1:1, 2:1, 3:1, to 4:1 to allow the child to acclimate to the increasing concentration of fat (Bergqvist *et al*., 2005). Evidence also exists that the KD can be started at

full calories at a ratio of 4:1 on day 1, with no prolongation of hospital stay, increased adverse effects, or decreased efficacy at 3 months (Bansal *et al*., 2014).

Table3: Nutritional Breakdown for Day 1(Thomas and Jeannette, 2017).

Breakfast: Scrambled Eggs with Cheese, Side of Bacon, Side of Spinach	• 2 Eggs (50g/each): 1.2g net carbs, 10g fat, 12g protein • 2 Slices of Bacon (8g/each): 1g net carbs, 9g fat, 5g protein • 1 Slice American Cheese (28g): 0.2g carbs, 6.5g fat, 6g protein • 1 Cup Spinach (30g): 0.4g net carbs, 0.1g fat, 0.9g protein
Snack : Almonds	• 1 Ounce Serving Almonds (28g): 2.5g net carbs, 14g fat, 6g protein
Lunch: Mackerel Fillet Searedin Olive Oil	• 1 Mackerel Fillet (100g): 0g carbs, 25g fat, 19g protein • 2 Tablespoons Olive Oil (40g): 0g carbs, 28g fat, 0g protein
Snack: Avocado	• 1 Avocado (200g): 4g net carbs, 29g fat, 4g protein
Dinner: Steak with a Side ofBrocolli	• 8 Ounce Steak (224g): 0g carbs, 48g fat, 62g protein • 1 Serving Brocolli (148g): 6.2g net carbs, 0.5g fat, 4.2g protein
Dessert: Sugar-free Gelatin Dessert Cup	• 1 Cup Sugar-free Gelatin (90g): 0g carbs, 0g fat, 1g protein • 2 Tablespoons Cool-Whip (18g): 2g net carbs, 3g fat, 0g protein

II.3 Supplementation

Due to the limited quantities of fruits, vegetables, enriched grains, and foods containing calcium in KDT, supplementation is essential, especially for B vitamins. Carbohydrate-free multivitamin and mineral products should be used. There is insufficient vitamin D and calcium in KDT food and coupled with the evidence for decreased vitamin D levels in children with epilepsy, that leads to the suggestion that both vitamin D and calcium should be provided at the recommended daily allowance (Vestergaard, 2015; Bergqvist *et al*., 2007).

Table4: Typical ketogenic diet initiation regimen (Hartman and Eileen Vining, 2007).

Before diet
Nutrition history obtained
Minimize carbohydrate intake for 1 day
Fasting begins after dinner the evening prior to admission
Day 1
Admission to the hospital
Conversion to carbohydrate-free medications
Basic laboratory results obtained if not done previously (metabolic profile, urine calcium, urine creatinine,
fasting lipid profile, antiepileptic drug levels)
Check finger-stick glucose every 6 hr; if <40 mg/dL, check every 2 hr
If symptomatic, or glucose <25 mg/dl, give 30 ml orange juice, measure blood glucose again
Parents begin classes
At dinner, one third of the calculated ketogenic meal given as "eggnog" (e.g., if the full meal is calculated as 150 ml, give 50 ml at this meal)
Blood glucose checks discontinued after dinner
Day 2
At breakfast and lunch, one-third of the calculated ketogenic meal given as "eggnog"
Symptomatic ketosis (e.g., nausea, vomiting) can be relieved with small quantities of orange juice
Parent classes continue
At dinner, two-thirds of the calculated ketogenic meal given as "eggnog"
Day 3
At breakfast and lunch, two-thirds of the calculated ketogenic meal given as "eggnog"
Parent classes conclude
At dinner, the first full ketogenic meal is given (not "eggnog")
Day 4
After breakfast (full ketogenic meal), the patient is discharged to home
Prescriptions written for carbohydrate-free medications, urine ketone test strips, a sugar-free, fat-soluble multivitamin
and calcium supplements, citrate salts (if indicated)
Clinic follow-up appointment arranged

II.4 Ketone Body Supplementation

As low-carbohydrate / ketogenic diets require high fat consumption and present difficulty with long-term adherence, alternative methods for targeting ketosis as a potential intervention for weight loss or as an ergogenic aid are required. In support of these, several studies examined the benefits of ketone body supplements on exercise performance (Cox *et al*., 2016; Scott *et al*., 2019; Leckey *et al*., 2017). Ketone body supplements are commercially available and commonly present in the form of ketone salts (KS) or ketone esters (KE). Additionally, medium chain triglycerides (MCT) are sometimes used to induce ketosis (Harvey *et al*., 2018) or are combined with KS to maximize the ketotic response (Kesl *et al*., 2016).

The formulation of KS may include βOHB or 1, 3-butandeniol (BD), bound to sodium, potassium, or calcium. There are a few potential concerns with consuming KS. First, βOHB in the salt form could include both D and L enantiomers of βOHB. Since D-βOHB is the biologically active form, approximately 50% of elevated serum βOHB levels are due to the presence of the non-metabolizable L-βOHB that must be excreted via the urinary system (Stubbs *et al*., 2017). As such, KS appears less effective at elevating serum βOHB comparatively (Kesl *et al*., 2016; Stubbs *et al*., 2017). Second, BD is a compound that must be converted to βOHB in the liver via dehydrogenase enzymes (Tate *et al*., 1971), which may result in delays in increased serum βOHB concentration (Kesl *et al*., 2016). Finally, the increased consumption of mineral salts, particularly sodium, may adversely affect blood pressure. In the last few years, most research studies utilized KE, which appears to be the most effective method to cause immediate and sustained increases in serum ketone bodies. There are several formulations of KE supplements, but the most identifiable is the (R)-3-hydroxybutyl (R)-3-hydroxybutyrate ketone monoester, which converts to in D-βOHB and BD upon ingestion (Clarke *et al*., 2012). This particular KE, when taken in combination with CHO, results in a 2% increase in exercise performance in trained cyclists (Cox *et al*., 2016). However, not all KE supplements increase exercise performance (Dearlove *et al*., 2019; Leckey *et al*., 2017), calling into question whether the precise formulation of the KE is essential or whether an additional substrate like CHO is required.

Of note, the available studies focused on exercise performance in trained endurance athletes, so whether supplementation in recreational athletes or fitness enthusiasts is appropriate is not known (Kristin *et al*., 2019).

II.5 Mechanism of action

The exact mechanism of action of the diet is still unknown though there are a number of theories and ongoing research. Likely, the KD works through multiple mechanisms. It is unlikely that these numerous hypotheses can be unified into a final common pathway; nevertheless, it is important to consider each of these putative mechanisms and discuss the evidence (Radhika Dhamija *et al*., 2013).

II.5.1 Importance of ketones

The ketones may have direct antiepileptic activity or may act to stabilize neuronal membranes. The earliest demonstration of direct *in vivo* effects of ketone bodies was made in the early 1930s when it was determined that acetoacetate, when administered intraperitoneally in rabbits, prevented seizures induced by thujone, a convulsant and an antagonist of $GABA_A$

receptors (Rho JM *et al*., 2002). Mice models for Dravet syndrome and genetic epilepsy with febrile seizures plus have been studied using the KD. Higher levels of β-hydroxybutyrate have been found in the mice with better seizure control compared to the mice treated with standard diet suggesting that ketones might have antiepileptic effects (Dutton *et al*., 2011). It has been shown in rat models that higher ratios of ketogenic diet (6:1), are more efficacious than traditional 4:1 ratio without more neurotoxic effects (Bough *et al*., 2000). However, as discussed previously, human data suggests that the MAD and LGIT have efficacy similar to traditional KD even with a lower degree of ketosis; suggesting high ketosis may not be major mechanism in humans (Chen and Kossoff, 2000;Coppola *et al*., 2011 ;Klein *et al*., 2010).

II.5.2 Role of polyunsaturated acids (PUFAs)

It is hypothesized that specific polyunsaturated fatty acids regulate neuronal membrane excitability by blocking voltage gated sodium or calcium channels (Stafstrom and Rho, 2012). In a study comparing the blood levels of arachidonate (PUFA) before and three to four weeks after starting the KD in children, higher levels of arachidonate correlated with improved seizure control. Thus, elevated PUFA may represent a potential anticonvulsant mechanism of the KD (Fraser *et al*., 2003). However there are other clinical trials on humans which have not supported this concept and the results show discrepancies (Auvin, 2012). In a prospective randomized study on adults with uncontrolled epilepsy who were randomized to either mineral oil (placebo) n= 9 or EPA (eicosapentaenoic acid) and DHA (docosahexaenoic acid) (ratio of 3:2) n=12; none on the n-3 PUFA versus two on the placebo diet had at least a 50% decrease in seizure frequency from baseline (Bromfield *et al*., 2008). Another 12-week, double-blind crossover trial, showed no significant benefits of daily supplementation of EPA and DHA vs. placebo in patients with intractable epilepsy (DeGiorgio *et al*., 2008).

II.5.3 Anti-inflammatory and protection against excitotoxicity

Several theories have suggested that the KD has anti-inflammatory effects and protects against excitotoxicity-mediatedneuronal cell death (Jeong *et al*., 2011). It has been shown in hippocampal cell lines to interfere with glutamate-mediatedtoxicity, a major mechanism underlying neuronal injury (Noh *et al*., 2006).

II.5.4 Alteration in neuro-metabolites and/or their receptors

The KD can potentially alter the levels of neuro-metabolites and influence seizure control (Dahlin *et al*., 2012). *In-vivo* studies have shown that β-hydroxybutyrate increases the brain

synthesis of kynurenic acid, an endogenous antagonist of glutamatergic and α7-nicotinic receptors, thus potentially acting as an anticonvulsant (Chmiel-Perzynska *et al*., 2011). In one study, the addition of either acetoacetate or β-hydroxybutyrate was associated with diminished consumption of glutamate via transamination to aspartate and increased formation of labeled GABA (Daikhin and Yudkoff, 1998). Recent positron emission tomography studies using flumazenil have suggested that KD may control seizures by directly or indirectly increasing the binding potential of the benzodiazepine receptors (Kumada *et al*., 2012).

II.5.5 Positive energy balance

A study on rat brain reported that the KD increased the total quantity of bioenergetic substrates (such as adenosine triphosphate (ATP)) leading to stabilization of the cell membrane. This can be potentially protective in states of high energy demand like seizures (DeVivo *et al*., 1978).

II.5.6 Antioxidant mechanisms

Ketone bodies have been shown to reduce the amount of coenzyme Q semiquinone, thereby decreasing free radical production. The KD also induces glutathione peroxidase activity in the rat hippocampus. Glutathione peroxidase is an enzyme found in erythrocytes that prevents lipid peroxidation (Veech, 2004; Ziegler *et al*., 2003).

II.6 Indicators of efficacy

Aspects of the diet that are crucial to efficacy would be useful to know in order to optimize outcomes while minimizing the impact these diets have on patients and their families (Vining, 1999). Variables that can be adjusted include calories, ratio of fat to carbohydrate, quality of fats or carbohydrates, schedules during seizure exacerbations, and timing of meals (Vining, 1999). The most common way to measure adherence to the ketogenic diet regimen is urine ketones (specifically, β-hydroxybutyrate, and acetoacetate), an easy and relatively cost-effective indicator of ketosis. In the classical ketogenic diet studies have failed to support a correlation between anticonvulsant efficacy and levels of the major ketone body β-hydroxybutyrate in the urine (Ross *et al*., 1985), and serum (Fraser *et al*., 2003). Urine ketones measured on dipsticks at the highest level can be consistent with serum β-hydroxybutyrate levels anywhere from 2 to 12 mmol/L (Gilbert *et al*., 2000). Serum levels might correlate with an anticonvulsant effect somewhat better than urine (Gilbert *et al*., 2000). One study of the medium chain triglyceride version of the diet (MCT-KD) suggested a threshold effect, wherein a certain level of plasma β-hydroxybutyrate and acetoacetate (the other major ketone body

produced during the ketogenic diet and starvation) might be necessary for an adequate anticonvulsant effect (Huttenlocher, 1976). However, another study comparing the classical MCT-KD, and a modified MCT-KD (the Radcliffe Infirmary diet) failed to show a correlation between ketone levels and seizure control (Schwartz *et al*., 1989b). Ketonemia and ketonuria (specifically measuring β-hydroxybutyrate and acetoacetate) therefore, probably serve as better indicators of adherence than efficacy. The suggestion of a threshold effect of these ketone bodies is suggested by data from some studies, but ketonuria probably serves as a surrogate (rather than a direct) marker of adherence, rather than efficacy. Degree of ketonuria does not correlate with seizure control on the Atkins diet (Kossoff *et al*., 2006). Acetone is the third major ketone body formed in patients consuming a ketogenic diet. It is formed by the spontaneous decomposition of acetoacetate, and is highly volatile, making its measurement a challenge. Nonetheless, acetone possesses anticonvulsant properties, so its measurement might serve as an indicator of efficacy (Likhodii *et al*., 2003). Using technology based on breathalyzers for detecting alcohol levels in drivers, breath acetone correlated with plasma levels of all three ketone bodies in patients with epilepsy on the ketogenic diet, although there was no correlation with seizure activity (Musa-Veloso *et al*., 2006). In a brain magnetic resonance spectroscopy study, not all patients whose seizures were controlled had elevated brain levels of acetone (Seymour *et al*., 1999). Thus far, it does not appear that acetone levels correlate with levels of seizure control. One tool readily available in neurology centers is EEG. Studies have failed to correlate consistent EEG changes with seizure protection in most patients consuming the ketogenic diet (Huttenlocher *et al*., 1971; Schwartz *et al*., 1989a; Vining *et al*., 1998; Fraser *et al*., 2003). Data from one study suggested EEG correlation with efficacy might be dependent on seizure type (Janaki *et al*., 1976; Vining, 1999). Early improvements in EEG were not sustained in another study of children with atypical absence epilepsy, despite clinical improvements in two-thirds of the patients (Ross *et al*., 1985). One major exception to this notion is that the EEG pattern of hypsarrhythmia may improve in patients with infantile spasms on the ketogenic diet; whether this is a direct effect of the diet or part of the natural history of the disorder remains to be determined (Kossoff *et al*., 2002b).

II.7 Side effects

The ketogenic diet is not a benign therapy, being associated with a number of side effects. Some effects are very predictable, preventable, and potentially treatable, such as dehydration and hypoglycemia (Ballaban-Gil, *et al*., 1998; Vining, 1999; Kang *et al*., 2004). Most patients have a mild acidosis at baseline. Other effects have been the subjects of isolated case reports,

so while serving a cautionary function, their consistent relationship to the ketogenic diet is unknown (e.g., cardiomyopathy, renal tubular acidosis). An example of a consistently noted side effect is nephrolithiasis, seen in 6% of patients on the ketogenic diet (Furth *et al*., 2000). Effects of the diet, especially hypocitruria, hypercalciuria, and aciduria, contribute to stone formation (most commonly consisting of urate or calcium). All patients now are screened for a family history of nephrolithiasis and for hypercalciuria (before starting the diet) with a urine calcium/creatinine ratio (>0.2 is considered abnormal). Patients with an elevated calcium/creatinine ratio, hematuria, or those taking carbonic anhydrase inhibitors (e.g., topiramate, zonisamide, or acetazolamide) with a concomitant personal or family history of nephrolithiasis are prescribed oral citrate salts as prophylaxis (e.g., Polycitra K, McNeil, San Bruno, CA, U.S.A.) (Kossoff *et al*., 2002a). Nephrolithiasis is treated by increasing fluid intake, alkalinization of urine, and discontinuation of carbonic anhydrase inhibitors; depending on the patient's symptoms, timely referral is made to Urology. Anticipated effects, such as lipid abnormalities, may not have short-term effects, but the relevance of this finding (in children typically exposed to the diet for only 2 yr) is unknown over the lifetime of a patient (Kwiterovich *et al*., 2003). Growth (height and weight) may be impaired, an effect most noticed in younger children (Vining *et al*., 2002; Liu *et al*., 2003). Put into perspective, the most common side effects of the diet are routinely monitored during follow-up clinic visits (e.g., at 3 and 6 months) that include laboratory work (serum chemistries, blood counts, fasting lipids, urinalysis, and urine calcium/creatinine ratio). Growth is monitored closely. Vitamin and mineral supplementation is provided to prevent known deficiencies. Gastrointestinal complaints can be treated with fluid intake, dietary adjustments, and laxatives (Sinha and Kossoff, 2005). During the diet initiation admission, families are counseled about signs and symptoms of possible side effects. Of great concern is effects that may not have an immediate manifestation, but could have implications for the patients' long-term health. We do not know if there is a 'vulnerable period' of exposure to the ketogenic diet for a limited (or extended) time. This could have implications for the health of the vasculature (e.g., atherosclerosis), bone (e.g., osteoporosis), liver (with its major role in ketogenesis), and muscle (a major storehouse of mitochondria in the body). The long-term complications in children maintained on KDT for >2 years have not been reviewed systematically; there is only one report in the literature looking at this small subgroup (Groesbeck *et al*., 2006).In this population, there was a higher risk of bone fractures, kidney stones, and decreased growth, but dyslipidemia was not identified (Groesbeck *et al*., 2006).

II.8 Duration of ketogenic diet

There is no consensus regarding the optimal duration of KD for management of obesity or diabetes (Kossoff, 2008). This decision must be individualized, based upon therapeutic goals, health status, and ability/willingness of the patient to conform to the suggested therapeutic diet. Well-conducted studies report safety over 2 years of use (Moreno *et al*., 2016), though the diet can be continued for longer to take advantage of its metabolic benefits.

The recommendation of trying the diet for a minimum period of two to three months, with achievement of at least moderate (> 80–160 mg/dl) urinary ketosis to determine if the diet will be effective. If the diet is effective, it is usually continued for one to two years, and then gradually weaned. There is considerable variation in practice for the duration of use of KD. In certain syndromes that are likely to relapse after diet weaning, long-term use of ketogenic diet is done. Successful use of KD for as long as 12 years in children has been published (Groesbeck *et al*., 2006). In such cases gradual transition of the diet to modified Atkins diet or low glycemic index treatment can be done. The side effects of the long-term use of the diet must be carefully weighed against the risk of discontinuation of the diet in patients with intractable epilepsy (Radhika Dhamija *et al*., 2013).

Chapter III

Ketogenic Diet for treatment of diseases

Chapter III: Ketogenic Diet for treatment of diseases

The ketogenic diet was initially established in the 1920s to be used in refractory epilepsy therapy (Pinto *et al*., 2018; Huttenlocher, 1976). To date, there are pieces of evidence showing that it has gained interest as a potential therapy for neurodegenerative disorders, such as AD (Van der Auwera *et al*., 2005; Reger *et al*., 2004), Parkinson's disease (VanItallie *et al*., 2005), and insulin resistance in type 2 diabetes (Augustin *et al*., 2018). Moreover, because of altered glucose metabolism, it may have anti-tumor effects, as well as, for example, in glaucoma (Zarnowski *et al*., 2012), or gastric cancer (Otto *et al*., 2008).

III.1 Epilepsy

Worldwide, there are an estimated at least 65 million people living with epilepsy (Ngugi *et al*., 2010). Reported estimates of epilepsy occurrence vary substantially among populations studied, but, in sum, indicate that in developed countries, the annual incidence of epilepsy is nearly 50 per 100,000 population, whereas the prevalence approximates 700 per 100,000 (Hirtz *et al*., 2007). In low and middle-income countries, estimates of the corresponding rates are generally higher (Hauser, 1995; Kotsopoulos *et al*., 2002; Sander, 2003; Burneo *et al*., 2005; Preux & Druet-Cabanac, 2005; Ngugi *et al*., 2010).

The term ‘‘epilepsy’’ encompasses many specific conditions in which unprovoked seizures occur that may have varying etiology, risk factors, and manifestations (Commission on Epidemiology and Prognosis of the International League Against Epilepsy, 1993).

The International League Against Epilepsy (ILAE) has proposed both conceptual and operational definitions of epilepsy. In 2005, the following definition of epilepsy was proposed: ‘‘a disorder characterized by an enduring predisposition to generate epileptic seizures and by neurobiologic, cognitive, psychological and social consequences of this condition. The definition requires the occurrence of at least one epileptic seizure’’ (Fisher *et al*., 2005).

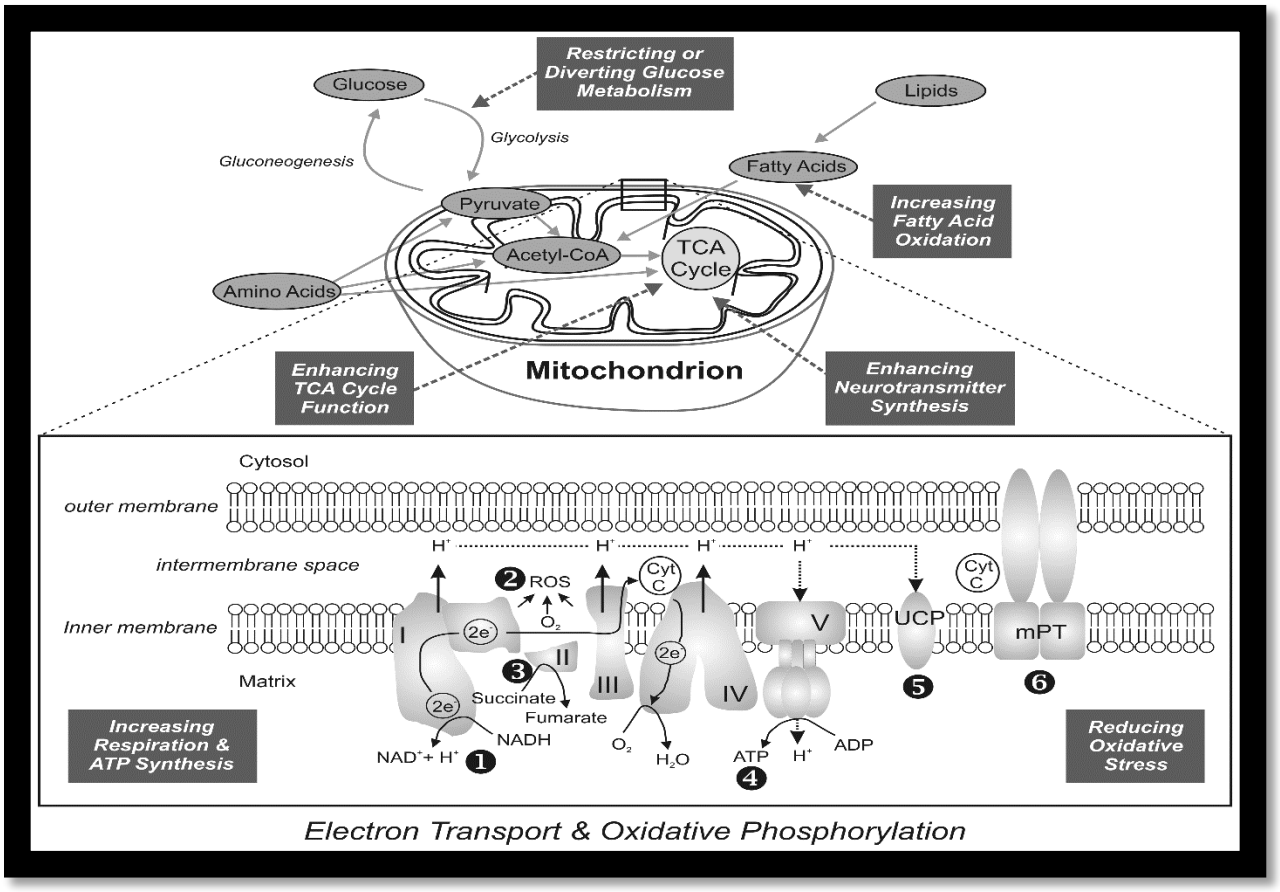

Figure 3: Major changes in important biochemical pathways reported to exert anticonvulsant and anti-epileptogenic effects in experimental models (Masino and Rho, 2012).

Putative interactions between mitochondrial respiratory complexes (MRCs) and KD-related metabolites. First ❶,either acetoacetate (ACA) or β-hydroxybutyrate (BHB) can oxidize the NADH couple. Second ❷, ketone bodies (KB) can decrease mitochondrial reactive oxygen species (ROS) generation. Third ❸, KB can protect neurons against MRC I & II inhibitors. Also, the KD elevates seizure threshold in epileptic patients with impaired MRC function. Fourth ❹, either the KD or KB can enhance ATP production. Fifth ❺, fatty acids can activate mitochondrial uncoupling proteins (UCPs). Finally❻, KB can elevate the threshold for mitochondrial permeability transition (mPT) activation. The bulk of experimental evidence supports the hypothesis that activation of mKATP channels decreases ROS formation, likely by diminishing the proton-motive force (Δψ) across the mitochondrial inner membrane (via transmembrane flux of potassium), and subsequently attenuating electron flux across the MRC, in a manner similar to mitochondrial uncoupling. Abbreviation: Cyt C, cytochrome c.

III.1.1The Ketogenic Diet and Epilepsy

The ketogenic diet (KD) is a high-fat, low-carbohydrate, adequate protein diet that has been employed as a treatment for medically-refractory epilepsy for over 90 years (Wilder RM, 1921). This "alternative" therapy was originally designed to mimic the biochemical changes associated with fasting (Figure 3), a treatment reported anecdotally over millennia to control seizure activity. The hallmark features of KD treatment are the production of ketone bodies (principally β-hydroxybutyrate, acetoacetate and acetone) – products of fatty acid oxidation in the liver – and reduced blood glucose levels. Ketone bodies provide an alternative substrate to

glucose for energy utilization, and, in the developing brain, also constitute essential building blocks for the biosynthesis of cell membranes and lipids (Masino and Rho, 2012).

Today, the KD is acknowledged as a proven therapy for epilepsy (Neal EG *et al*., 2009). The growing number of clinical KD treatment centers throughout the world serves as a testament to the notion that irrespective of cultural and ethnic differences that define dietary and nutritional practices, a fundamental shift from carbohydrate-based consumption to fatty acid oxidation results in similar clinical effects, Figure 4 shows the Metabolic pathways involved in ketogenic diet (KD) treatment. Despite such broad use, surprisingly little is understood about its underlying mechanisms of action. This may be due to the inherently complex interplay between the network dynamics of the human brain (particularly in the disease state and during development), and the myriad biochemical and physiological changes evoked by consumption of dietary substrates. It has not been straightforward to determine cause-and-effect relationships in this bewildering context, and one cannot be certain whether specific molecular and cellular alterations observed are relevant or simply represent epiphenomena. This knowledge gap has hindered efforts to develop improved or simplified treatments (such as a "KD in a pill"3) that obviate the strict adherence to protocol that the KD requires. However, research efforts have been intensifying over the past decade, and recent investigations have provided new insights and molecular targets (Masino and Rho, 2012).

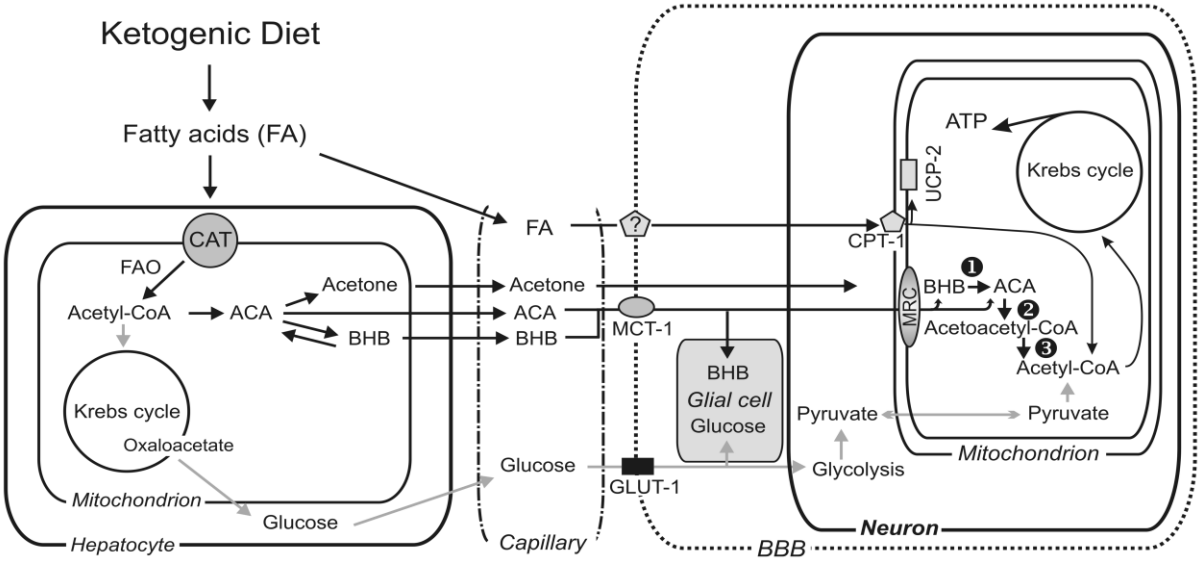

Figure 4: Metabolic pathways involved in ketogenic diet treatment (Masino and Rho, 2012).

In the liver, fatty acids are ordinarily converted into acetyl-CoA which enters the tricarboxylic acid (TCA) cycle. When fatty acid levels are elevated and exceed the metabolic capacity of the TCA cycle, acetyl-CoA is shunted to ketogenesis. Two acetyl-CoAs can combine through a thiolase enzyme to produce acetoacetyl-CoA, which is a precursor for the synthesis of acetoacetate (ACA) and β-hydroxybutyrate (BHB). Acetone, the other major ketone body, is produced primarily from spontaneous decarboxylation of ACA, and can be eliminated as a volatile substrate through the lungs and kidneys. In the blood, ACA and BHB are transported from the vascular lumen to the brain interstitial space, and to both glia and neurons, by monocarboxylic acid transporters (MCTs). MCT-1 is the principal carrier localized to the vascular endothelium. Within neurons, both ACA and BHB are transported directly into mitochondria, and then converted to acetyl-CoA through several enzymatic steps. BHB is converted to ACA through D-β-hydroxybutyrate dehydrogenase, and ACA undergoes subsequent conversion to acetoacetyl-CoA through a succinyl-CoA transferase enzyme. Finally, acetoacetyl-CoA-thiolase converts acetoacetyl-CoA to two acetyl-CoA moieties which then enter the TCA cycle. Abbreviations: CAT (carnitine-acylcarnitine translocase), FAO (fatty acid oxidation), ACA (acetoacetate), BHB (β-hydroxybutyrate), MCT-1 (monocarboxylate transporter-1), GLUT-1 (glucose transporter-1), BBB (blood-brain barrier), CPT-1 (carnitine palmitoyl transferase), UCP (uncoupling protein), ATP (adenosine triphosphate), ❶(3-hydroxybutyrate dehydrogenase), ❷ (succinyl-CoA3-oxoacid CoA transferase), ❸ (mitochondrial acetoacetyl-CoA thiolase).

III.1.2 Anticonvulsant mechanisms of the Ketogenic Diet

Since the KD was originated over 85 years ago, several major hypotheses have been advanced, but none have been widely accepted. Several key aspects of the KD might ultimately result in seizure protection. Ketone bodies, free fatty acids (in particular, polyunsaturated fatty acids), or glucose restriction might each lead directly or indirectly to seizure control. While it is possible that any one of these KD-induced changes is responsible for the anticonvulsant action of the KD (Figure 6), available evidence suggests that improved seizure control, at a minimum, likely requires all three (Kristopher and Jong, 2007).

III.1.3 Role of ketone bodies

Beta-hydroxybutyrate (BHB) is the predominant ketone body measured in the blood, and as such, has been used as a clinical measure of KD implementation. Accordingly, nearly all KD studies have attempted to establish a causative link between ketonemia and anticonvulsant efficacy, Figure 5 shows the Production of ketone bodies and potential primary anticonvulsant mechanisms. Although robust elevations in plasma BHB levels have been observed during KD treatment (Bough *et al*., 1999; Thavendiranathan *et al*., 2000), there is no significant correlation between plasma BHB levels and seizure protection. Optimal seizure protection generally lags days to weeks behind the development of ketonemia, which occurs within hours of KD onset (Kristopher and Jong, 2007).

Nevertheless, there is some evidence that ketones other than BHB may possess anticonvulsant properties. When injected into animals, acetone and its parent acetoacetate (ACA), prevent acutely provoked seizures. Seminal work in the 1930s revealed that acute intraperitoneal administration of acetone or ethyl-acetoacetate protected rabbits from thujone-induced seizures (Helmholz and Keith, 1930; Keith, 1933).

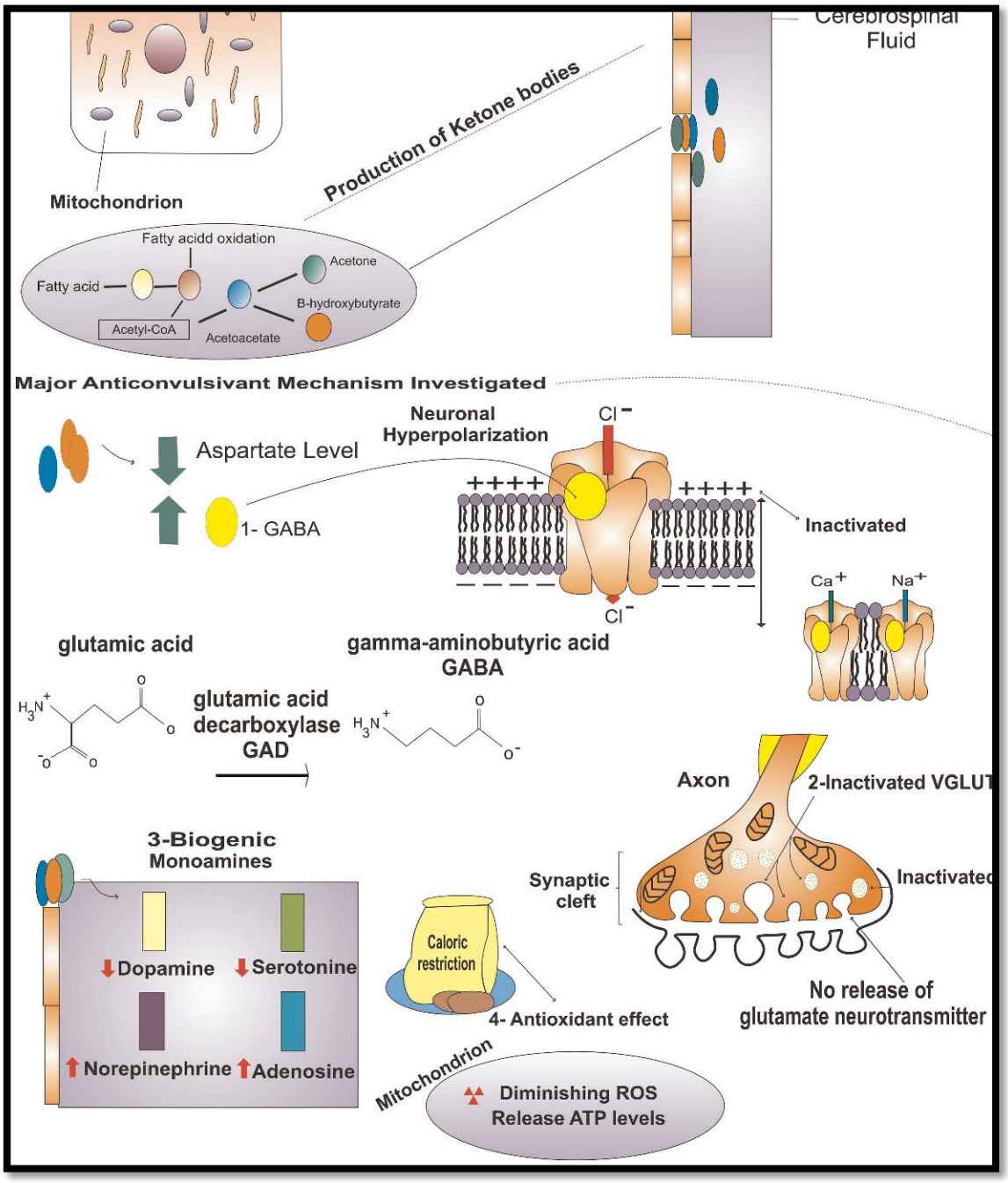

Figure 5: Production of keton bodies and potential primary anticonvulsant mechanisms (Patricia Azevedo de Lima *et al*., 2014).

(1) GABA neurotransmitter (neuronal hyperpolarization and membrane channels; (2) inactivation of VGLUT and inhibition of glutamate neurotransmitter; (3) modified concentrations of biogenic monoamines; and (4) antioxidant mechanism of diminishing reactive oxygen species.

III.1.4 Role of glucose restriction

Whereas most studies have suggested that persistent ketosis is essential to KD-induced seizure protection, others have posited that glucose restriction is the key feature (Greene *et al*., 2003). In addition to ketosis, it is clear that as ketonemia develops, another immediate consequence of CR and/or KDs is a ‘moderate’ reduction in blood glucose. Does caloric

restriction simply act to limit gluconeogenic substrates that would otherwise reduce KD ratio and counter efficacy? Or, might glucose restriction result in another metabolic adaptation that helps quell aberrant hyperexcitability? Calorie restriction alone was sufficient to retard seizure susceptibility in juvenile and adult epileptic EL mice; and, blood glucose levels were inversely correlated with a decreased risk of seizures (Greene *et al*., 2001). Greene *et al*. (2003) hypothesized that CR reduces energy production through glycolysis, which limits a neuron's ability to reach (and maintain) high levels of synaptic activity necessary for seizure genesis (Kristopher and Jong, 2007).

Others have hypothesized that glucose restriction during KD treatment activates ATP-sensitive potassium (K_{ATP}) channels (Schwartzkroin, 1999; Vamecq *et al*., 2005). Interestingly, K_{ATP} channels are ligand-gated receptors broadly expressed throughout the central nervous system, in both neurons and glia (Thomzig *et al*., 2005). These channels act as metabolic sensors, linking cellular membrane excitability to fluctuating levels of ADP and ATP. Activation of this receptor by reduced ATP/ADP ratios opens the channel and leads to membrane hyperpolarization. When glucose is limited (e.g., during administration of a classic KD, which is typically CR by 25%), K_{ATP} channels might open to hyperpolarize the cell as the intracellular ATP concentrations fall. Conversely, when glucose is present and ATP concentrations rise, K_{ATP} channels close. As such, K_{ATP} channels may provide a measure of protection against a variety of metabolic stressors such as hypoxia, ischemia, and hypoglycemia, and are believed to regulate seizure threshold (Seino and Miki, 2003).

III.1.5 Role of fatty acids

Polyunsaturated fatty acids (PUFAs) such as docosahexanoic acid (DHA, C22:6ω3), arachidonic acid (AA, C20:4ω6), or eicosapentanoic acid (EPA, C20:5ω3) are believed to affect profoundly cardiovascular function and health (Leaf and Kang, 1996; Nordoy, 1999; Leaf *et al*., 2003). In cardiac myocytes, PUFAs inhibited fast, voltagegated sodium channels (Xiao *et al*., 1998) and L-type calcium channels (Xiao *et al*., 1997). Similar findings have been observed in neuronal tissue. For example, DHA and EPA diminished neuronal excitability and bursting in hippocampus (Xiao and Li, 1999). It is not surprising then that PUFAs are becoming an increasingly popular focus of KD research. After KD treatment, specific PUFAs (i.e., AA and DHA) were found to be elevated in both serum (Cunnane *et al*., 2002; Fraser *et al*., 2003) and brain (Taha *et al*., 2005) of patients and animals. Importantly, one report documented that the rise (or drop) in total fatty acids during KD treatment closely paralleled clinical improvement

(or loss) of seizure control (Dekaban, 1966). An additional study found that dietary supplementation with 5 g of (65%) n-3 PUFAs once per day produced a marked reduction in seizure frequency and intensity in a few epileptic patients (Schlanger *et al*., 2002). These findings suggest that KD-induced elevations in PUFAs such as DHA and/or AA might act directly to limit neuronal excitability and dampen seizure activity (Kristopher and Jong, 2007).

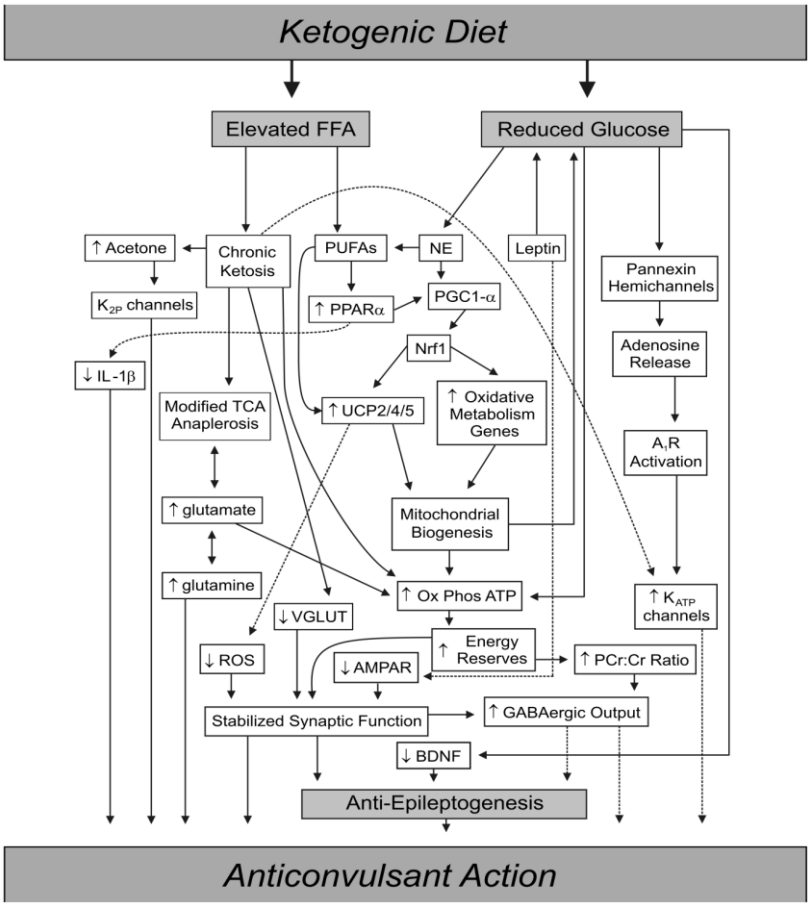

Figure 6: Hypothetical pathways leading to the anticonvulsant effects of the ketogenic diet (Bough and Rho, 2007).

Elevated free fatty acids (FFA) lead to chronic ketosis and increased concentrations of polyunsaturated fatty acids (PUFAs) in the brain. Chronic ketosis is predicted to lead to increased levels of acetone; this might activate K_{2P} channels to hyperpolarize neurons and limit neuronal excitability. Chronic ketosis is also anticipated to modify the tricarboxcylic acid (TCA) cycle, as would the presence of anaplerotic substrates such as triheptanoin. This would increase glutamate and, subsequently, GABA synthesis in brain. Among several direct inhibitory actions, PUFAs boost the activity of brain-specific uncoupling proteins (UCPs). This is expected to limit ROS generation, neuronal dysfunction, and resultant neurodegeneration. Acting via the nuclear transcription factor peroxisome proliferator-activated receptor-α (PPARα) and its co-activator peroxisome proliferator-activated receptor γ coactivator-1 (PGC-1α), PUFAs would induce the expression of UCPs and coordinately up-regulate several dozen genes related to oxidative energy metabolism. PPARα expression is inversely correlated with IL-1β cytokine expression; given the role of IL-1β in hyperexcitability and seizure generation, diminished expression of IL-β cytokines during KD treatment could lead to improved seizure control. Ultimately, PUFAs would stimulate mitochondrial biogenesis. Mitochondrial biogenesis is predicted to increase ATP production capacity and enhance energy reserves, leading to stabilized synaptic function and improved seizure control. In particular, an elevated phosphocreatine:creatine (PCr:Cr) energy-reserve ratio is predicted to enhance GABAergic output, perhaps in conjunction with the ketosis-induced elevated GABA production, leading to diminished hyperexcitability. Reduced glucose coupled with

elevated free fatty acids are proposed to reduce glycolytic flux during KD, which would further be feedback inhibited by high concentrations of citrate and ATP produced during KD treatment. This would activate metabolic KATP channels. Ketones may also directly activate KATP channels. Reduced glucose alone under conditions of adequate or enhanced energy levels activate pannexin hemi-channels on CA3 pyramidal neurons, releasing ATP into the extracellular space; ATP is converted via ectonucleotidases to adenosine which subsequently activates adenosine receptors (A_1R). A_1R activation is also coupled to KATP channels. Ultimately, opening of KATP channels would hyperpolarize neurons and diminish neuronal excitability to contribute to the anticonvulsant (and perhaps neuroprotective actions of the KD). Increased leptin, seen with KD treatment, can reduce glucose levels and inhibit AMPA (α-amino-3-hydroxy-5-methyl-4-isoxazolepropionic acid) receptor-mediated synaptic excitation. Reduced glucose is also expected to down-regulate brain-derived neurotrophic factor (BDNF) and TrkB signaling in brain. As activation of TrkB pathways by BDNF have been shown to promote hyperexcitability and kindling, these potential KD-induced effects would be expected to limit the symptom (seizures) as well as epileptogenesis. Boxed variables depict findings described from KD studies; up (↑) or down (↓) arrows indicate the direction of the relationship between variables as a result of KD treatment. Dashed lines are used to clarify linkages and are not meant to suggest either magnitude or relative importance compared to solid lines. Adapted with permission from reference **(Bough and Rho, 2007)**.

III.2 Coronavirus disease 2019(COVID 19)

In December 2019, unexplained pneumonia (later named as coronavirus disease 2019, COVID 19) broke out in Wuhan, China (Hui and Madani, 2019; Zhu *et al*., 2020). The initial patient was related to a seafood wholesale market in Wuhan. A new type of coronavirus was isolated from human respiratory epithelial cells, which belongs to the subgenus Sabevirus of the subfamily Coronavirus (Harding and Lanese, 2020). Different from the previously isolated MERS CoV and SARS CoV, this virus is the seventh coronavirus that can infect humans and is named as SARS CoV 2 (Guo *et al*., 2020; Nie *et al*., 2020).

The number of coronaviruses that affect people and which are known up to now, being common all over the world, are seven. The most lethal of the known coronaviruses is MERS CoV, which often progresses to severe pneumonia and has an estimated mortality rate between 30% and 40%; SARS CoV causes fever, chills and body aches, and often progresses to pneumonia, a severe condition in which the lungs become inflamed and fill with pus; this virus has an estimated mortality rate of 9,6%; and the most recent, SARS CoV 2, has an estimated mortality rate of about 2,3% (Harding and Lanese, 2020).

III.2.1The Ketogenic Diet and Covid 19

III.2.1.1 Ketogenic diet as lifestyle behavior approach against Covid 19

Among lifestyle, behaviors it is surprising that nutritional advice are still poorly considered in public health discussions about the prevention or reduction of Sars Cov 2 infection risk and related complications. Thus, a call to action is needed, in order to promote proper nutrition strategies to improve the immune response and the potential clinical outcomes towards COVID 19 (Paoli *et al*., 2020).

Recently, Soliman *et al*. proposed a combination of intermittent fasting and supplementation in medium chain triglycerides as potential prophylactic strategies or adjuvant

therapy to tackle SARS CoV 2 infection, by means of a change in the host metabolic state from a carbohydrate-dependent glycolytic to a fat-dependent ketogenic state, aimed to alter viral replication (Soliman *et al*., 2020). Such metabolic shift causes an increased resistance to mitochondrial stress, an improvement in antioxidant defenses, an augmented autophagy and DNA repair, and a decreased insulin secretion (de Cabo and Mattson, 2019). In this context, ketogenic diets represent a nutritional approach with intriguing theoretical bases for improving the immunological response to Sars CoV 2 infection in high-risk populations (Sukkar, 2020).

III.2.1.2 Potential preventive effects of ketogenic diet on SARS CoV 2 infection

Ketogenic diet may play a role modulating both innate and adaptive immune cells, which synergistically protect the host against pathogens' assaults.

III.2.1.2.1 Innate cell mediated immunity

Innate immune cells are firstly triggered by viral antigens through the activation of pattern recognition receptors (PRRs), in order to inhibit viral replication and modulate the adaptive immunity (Bowie and Unterholzner, 2008). In this context, the NLRP3/ inflammasome is an important innate immunity sensor, mediating virus-induced inflammation through the induction of Interleukine-1β (IL-1β) and Interleukine-18 (IL-18) secretion (Franchi and Nunez, 2012). The pattern recognition receptor NLRP3 is a nucleotide oligomerization domain (Nod)-like receptor (NLR), that recognizes both damage-associated molecular patterns (DAMPs), such as toxins, ATP, excess of glucose, cholesterol crystals, and pathogen associated molecular patterns (PAMPs), such as viral and bacterial molecules. For instance, RNA viruses can activate NLRP3 through mitochondrial antiviral signaling protein (MAVS) on the mitochondrial outer membrane. Activated NLRP3 promotes the formation of the inflammasome complex interacting with the adaptor protein ASC (apoptosis-associated speck-like protein containing C-terminal caspase recruitment domain [CARD]), which, in turn, triggers the activation of the zymogen procaspase-1 into caspase-1. Finally, the inflammatory caspase-1 converts the inactive pro-Interleukine-1β (pro- IL-1β) and pro-Interleukine-18 (pro-IL-18) into their corresponding active proinflammatory cytokines (Swanson *et al*., 2019).

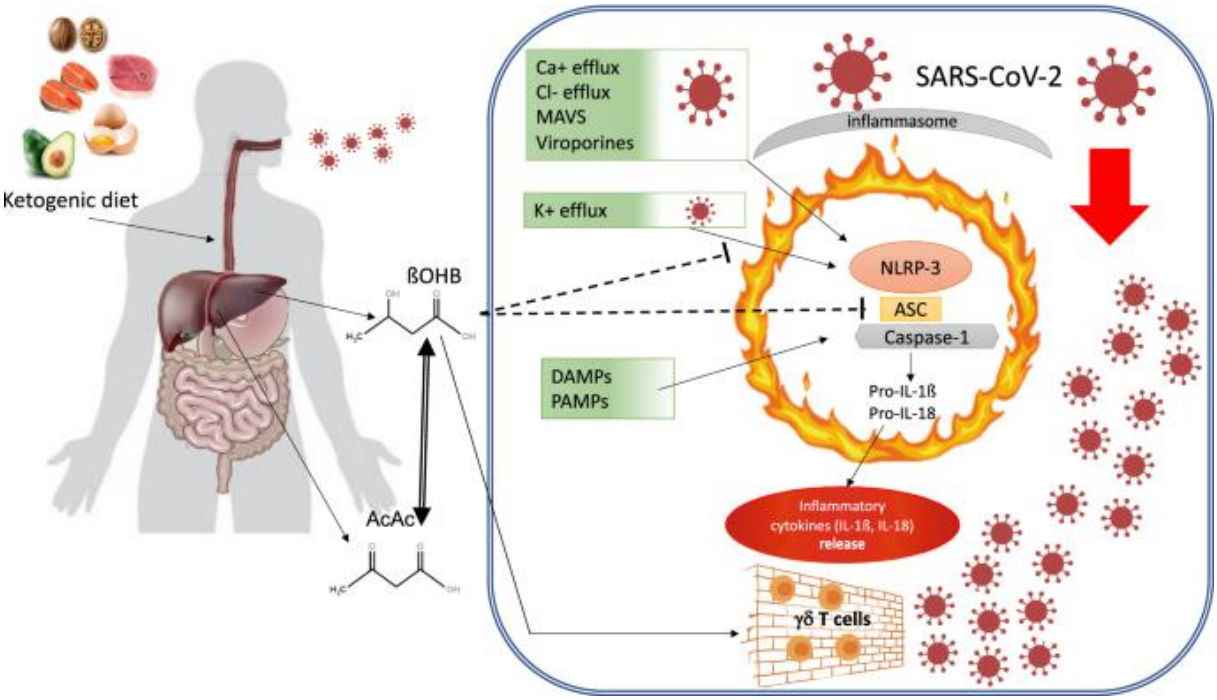

Figure 7: Ketone bodies and NLRP3/inflammasome activation (Paoli *et al*., 2020).

Protective effects of ketogenic diet and ßOHB on risk conditions associated with serious COVID-19 disease. ßOHB: Beta-hydroxybutyrate, AcAc: AcetoAcetate, MAVS: mitochondrial antiviral signalling protein, LPS: lipopolysaccharide, NLP3: NOD-, LRR- and pyrin domain-containing protein 3, ASC: Adaptor apoptosis associated Speck-like protein containing a Caspase Recruitment Domain (CARD), Pro-IL-1ß: pro-interleukin 1 beta, Pro-IL-18: pro-interleukin 18, DAMPs: damage-associated molecular patterns; PAMPs: pathogen-associated molecular patterns.

The NLRP3/inflammasome activation due to a viral infection has been documented for influenza A virus (IAV), encephalomyocarditis virus (EMCV), hepatitis C virus (HCV), and SARS-CoV, and seems to be mediated also by viral proteins known as viroporins, specific Molecules(Chen *et al*., 2019) which assemble into homo-oligomers and form hydrophilic pores across the cytosolic organelle membranes, thereby increasing Na+, K+, and Ca2+ flux. Increased intracellular Ca2+ concentration and reduced intracellular K + levels represent important triggering signals for NLRP3/inflammasome activation and the subsequent massive secretion of proinflammatory cytokines (Horng, 2014). All coronaviruses known so far, including the new spread SARS-CoV2, are able to encode for viroporines E and 3a and their expression is functional to the activation of NLRP3/inflammasome in COVID-19 disease (Chen *et al*., 2019).

There is growing evidence that ßOHB inhibits NLRP3/ inflammasome activation (Figure 7). The favorable effects of KD on inflammatory cytokines in humans (Paoli *et al*., 2015a), in animal and cellular models (Jeong *et al*., 2011) are well established. ßOHB is able to act on a central common signaling pathway, specific to the NLRP3/inflammasome, in response to many different pro inflammatory stimuli. More specifically, ßOHB inhibits NLRP3/inflammasome

activation through the reduction of K+ efflux from macrophages and the inhibition of the inflammasome assembly (Fig. 07). Consistent with these observations, ßOHB-dependent inhibition of IL-1β and IL-18 secretion in human monocytes has been documented (Youm *et al*., 2015).

In consideration of the role of inflammasome activation in triggering the systemic inflammatory cascade observed in COVID 19 patients (Mehta *et al*., 2020), approaches based on increasing plasma ßOHB, such as KDs, should be taken into account to prevent the development or the progression of the cytokine storm syndrome. Interestingly, a recent hypothesis paper underlined the importance of a drastic reduction of glucose oral supply, in order to reduce macrophage M1 polarization in the early stages of inflammation (Sukkar and Bassetti, 2020). In fact, the M1 phenotype, whose activation is linked to the cytokine storm syndrome (Huang *et al*., 2018), is strictly dependent upon aerobic glycolysis, which is known to be reduced by a drastic reduction in glucose uptake, as it occurs during a KD. On the other hand, KDs could sustain the metabolism of anti-inflammatory M2 macrophages, which abundantly express OXPHOS enzymes through the continuous supply of free fatty acids (Sukkar and Bassetti, 2020).

III.2.1.2.2 Adaptive cell mediated immunity

T lymphocytes recognize specific ligands by Tcell receptors (TCR), which are specialized in antigen recognition. In most species, the vast majority of T cells TCR is composed by an α and a β chain, and a minor Tcell population expresses a TCR characterized by γ and δ chains. In humans and mice most of T cells (> 90%) in peripheral blood and lymphoid organs express the TCR α/β chain and only a minority of T cells (< 10%) express the TCR γ/δ. Interestingly, in mice, γδ T cells are the most abundant Tcell population in epithelia and mucosa (Kaufmann, 1996). The epithelial layers display a peculiar immune system and resident T lymphocytes, which are in close contact with the epithelial cells. In humans, γδ T cells are enriched in skin and mucosa, suggesting a specific function for γδ T cells in mucosa layers (Kaufmann, 1996). Therefore, these cells may play an important role in viral infection surveillance and response in mucosal inner layers of the respiratory trait. A recent study by Goldberg *et al*. showed that immunocompetent mice exposed to intranasal challenge of influenza A virus (IAV), displayed better survival when their γδ T cell population were increased in the lung, determining an improvement of barrier function and anti-viral response (Goldberg *et al*., 2019). More specifically, mice underwent γδ T cell expansion by means of a ketogenic diet for 7 days, and displayed a better blood O2 saturation compared to control chow-fed mice, with an increased secretory function, mucus production in the airways, and IL-17 production, thereby mediating

anti-viral defense and tissue repair through regulatory T cells (Treg) activation, a cell population which is known to be reduced during the COVID 19 cytokine storm (Moore and June, 2020). Notably, γδ T cells expansion was specifically promoted by KD, since pharmacological increase of ßOHB failed to induce this phenotype (Goldberg *et al*., 2019), and only endogenous ketone bodies—not the exogenous ketone precursor 1,3-butanediol— were able to protect mice against influenza infection. Importantly, γδ T cells can expand in response to IAV and kill IAV-infected airway cells also in humans (Li *et al*., 2013). Therefore, KD could represent a valuable option in order to physiologically increase ßOHB levels, and optimize adaptive immune cells to prevent Sars Cov2 infection. A recent observation showed that γδ T cells are also expressed in adipose tissue (Kohlgruber *et al*., 2018), where they increase IL-17 production, thereby promoting the expansion of Treg cells function, with immuno-modulatory and anti-inflammatory properties. It is therefore tempting to speculate a key role for γδ T cells in maintaining barrier integrity against Sars Cov2 infection in the lung, as well as in adipose tissue, where meta-inflammation could enhance the cytokine reaction in response to viral infection. KD may represent a valid approach to specifically sustain these protective mechanisms (Paoli *et al*., 2020).

III.3 Alzheimer

Alzheimer's disease (AD) is the most significant cause of dementia that affects around 50 million people worldwide (Patterson, 2018). It is a heterogeneous and multifactorial disorder, characterized by cognitive impairment with a progressive decline in memory, disorientation, impaired self-care, and personality changes (Kelley and Petersen, 2007; Lange *et al*., 2017). The most common symptom present at the beginning of AD is associated with short term memory deficit, which affects daily activities (Lange *et al*., 2017). Cognitive deficits, resulting from the loss of neurons, are susceptible to neurofibrillary degeneration located in the limbic system, subcortical structures, archicortex and neocortex, and progressive synaptic dysfunction (Serrano-Pozo *et al*., 2011). Pathologically, AD involves progressive deposition of amyloid β-peptide (Aβ) as amyloid plaques, hyperphosphorylated tau protein intracellularly as neurofibrillary tangles (NFTs) and neuronal loss in the hippocampus (Kelley and Petersen, 2007). Moreover, patients with AD present mitochondrial dysfunction and metabolic changes, such as impaired glucose utilization in the brain (glucose hypometabolism) (Swerdlow, 2011). Mitochondrial dysfunction and a decline in respiratory chain function alter amyloid precursor protein (APP) processing, which leads to the production of the pathogenic amyloid-β fragments (Wilkins and Swerdlow, 2017; McDonald and Cervenka, 2018). On the other hand, the reduced glucose uptake and inefficient glycolysis have been strongly associated with progressive

cognitive deficiency (Castellano *et al*., 2015), due to the downregulation of the glucose transporter GLUT1 in the brain of patients with AD (Koppel and Swerdlow, 2018). Clinical studies have demonstrated an association between a high-glycemic diet and increased cerebral amyloid deposition in mice (Van der Auwera *et al*., 2005;Pawlosky *et al*., 2017) and humans (Taylor *et al*., 2017), suggesting that insulin resistance of brain tissue may contribute to the development of AD (de la Monte, 2017).

III.3.1 Etiopathogenesis of Alzheimer's disease

The etiology of AD remains not fully explained, but both genetic and environmental risk factors have been proposed to be involved. Thus, the etiopathogenesis of AD has been linked to hypometabolism (Costantini *et al*., 2008; Kashiwaya *et al*., 2013), mitochondrial dysfunction (Johri and Beal, 2012), inflammation (Takahashi *et al*., 2017; Akiyama *et al*., 2000), and oxidative stress (Pinto *et al*., 2018). Some more cellular events associated with AD neuropathogenesis include impairment of calcium homeostasis and disturbed autophagy (Takahashi *et al*., 2017). On the brain tissue level, neurons loss, brain atrophy, and cerebral amyloid angiopathy have to be mentioned (Takahashi *et al*., 2017). In addition, the systems-level characteristic for AD involves the blood-brain barrier (BBB) abnormalities, brain arteries atherosclerosis, and brain hypoperfusion (Takahashi *et al*., 2017). Moreover, genome-wide association studies (GWAS) have revealed that more than 20 genetic loci may be implicated with the risk of AD development (Guerreiro and Hardy, 2014). The primary gene is the apolipoprotein E (ApoE), and the epsilon 4 (E4) variant of ApoE was found to increase the risk for AD generation (Guerreiro and Hardy, 2014). Insulin resistance and type 2 diabetes mellitus are the essential risk factors of AD (Lange *et al*., 2017).

III.3.2 The Ketogenic Diet and Alzheimer's disease

III.3.2.1 The Impact of the Ketogenic Diet on Amyloid and Tau Protein

Defects in mitochondrial and respiratory chain function may alter APP processing, resulting in production neurotoxic Aβ (Zhang *et al*., 2011). The ketogenic diet could alleviate the effects of impaired glucose metabolism (Castellano *et al*., 2015; Broom *et al*., 2019) by providing ketones as alternative metabolic substrates for the brain. Besides, this diet may help to reduce the deposition of amyloid plaques by reversing the Aβ (1–42) toxicity (Broom *et al*., 2019; Kashiwaya *et al*., 2000). Studies suggest that KD may affect neuropathological and biochemical changes observed in AD. Rodents treated with the KD, exogenous β-OHB, and MCT display reduced brain Aβ levels, protection from amyloid-β toxicity, and improved mitochondrial function (Van der Auwera *et al*., 2005; Kashiwaya *et al*., 2013). In the transgenic mice model of AD, it was observed that KD made soluble Aβ deposits level in their brain 25%

less after only 40 days (Yudkoff *et al*., 2005). Also, in humans, this process may be determined by the presence or absence of the ApoE4 genotype; however, the presence of which is a risk factor for AD development (Reger *et al*., 2004; Henderson *et al*., 2009).

III.3.2.2 The Impact of the Ketogenic Diet on Inflammation

Inflammation and oxidative stress are two essential factors recognized in the neuropathology of AD, underlying neurotoxic mechanisms leading to neuronal loss, which is present in the brain regions responsible for memory and cognitive processes (Pinto *et al*., 2018; Verdile *et al*., 2015). It involves releasing proinflammatory cytokines, NO, and inhibition of neurotrophins, resulting in damage to surrounding tissues (Verdile *et al*., 2015).

Because a great proportion of cells in the immune system (e.g., macrophages or monocytes) express abundant GPR109A, KD may actually affect neuroinflammatory mechanisms (Yang *et al*., 2019). GPR109A, which was found in the brain tissue is, in fact, a G protein-coupled receptor known as hydroxy-carboxylic acid receptor 2 (HCA2) (Yang *et al*., 2019). Moreover, the β-OHB may directly bind to HCA2, which is expressed on microglia (Yang *et al*., 2019), dendritic cells, and macrophages (Taggart *et al*., 2005). Its activation induces the neuroprotective subset of macrophages, which depend on PGD2 production by COX1 (Taggart *et al*., 2005). Consequently, neuroinflammation is reduced (Yang *et al*., 2019). KD has also been proved to exert effects on inflammatory processes (Rahman *et al*., 2014) by inhibiting the activation of the nuclear factor kappa-light-chain-enhancer of activated B cells (NF-$_K$B). It results in the downregulation of COX2, and inducible nitric oxide synthase expression, associated with increased immune response (Cullingford, 2004). Moreover, the activity of cytokines, such as IL-1b, IL-6, CCL2/MCP-1, TNF-α, is diminished (Dupuis *et al*., 2015). Besides, peroxisome proliferator-activated receptor γ (PPARγ) can reduce the expression of NF-$_K$B, therefore alleviating the neuronal damage caused by excitotoxicity of N-methyl-D-aspartate (NMDA) (Liu and Hong, 2003; Picard *et al*., 2004).

Moreover, the KD diet influences the anti-inflammatory action via activation of microglial cells (Yang and Cheng, 2010), pro-apoptotic properties, and elevated concentrations of neuroprotective mediators, including neurotrophins {neurotrophin-3 (NT-3), brain-derived neurotrophic factor (BDNF) and glial cell line-derived neurotrophic factor (GDNF)}, and molecular chaperones (proteins preventing aggregation of polypeptides into potentially toxic molecules) (Włodarek, 2019; Maalouf *et al*., 2009).

Another mechanism of KD is the inhibition of histone deacetylases (HDACs), which play a role in altering chromatin structure, and accessibility (Pinto *et al*., 2018). β-OHB inhibits HDACs 1, 3, and 4 (class I and IIa) in vitro, leading to memory function improvement and

synaptic plasticity (Bough *et al*., 2006;Peixoto and Abel, 2013). Besides, ketones are able to inhibit the innate immune sensor NOD-like receptor 3 (NLRP3) inflammasome, which controls the activation of caspase-1, and the release of proinflammatory cytokines, such as IL-1β and IL-18 by limiting the K+ efflux from cells (McDonald and Cervenka, 2018;Veyrat-Durebex *et al*., 2018;Youm *et al*., 2015).

III.3.2.3 The Impact of the Ketogenic Diet on Dementia

The main symptom of some neurodegenerative disorders is dementia, and it includes thinking difficulties, loss of memory, and obstacles in problem solving. Progressive impairment of cognitive functions in AD patients was associated with a reduction in glucose uptake and metabolism (Castellano *et al*., 2015), especially if genetic risk factors for AD or positive family history are present. Another possible mechanism is that lower glucose uptake in the brain may contribute to the development of AD neuropathology (Paoli *et al*., 2014). The study of Vanitallie (Vanitallie, 2013) shows that an early disturbance in brain glucose metabolism can be detected before any measurable cognitive decline (Vanitallie, 2013). Moreover, it correlates with the downregulation of glucose transporter GLUT1 in people with AD (Winkler *et al*., 2015). It is observed that a high-glycemic diet is associated with increased insulin resistance and a higher risk of AD development (Taylor *et al*., 2017). Few studies have demonstrated that supplementation with MCT and KD improves cognitive performance (Reger *et al*., 2004;Henderson *et al*., 2009;Krikorian *et al*., 2012;Ota *et al*., 2019).

III.3.2.4 The Impact of the Ketogenic Diet on Neurodegeneration

AD is associated with energy imbalance caused by impaired glucose transport and metabolism and mitochondrial dysfunction. Energy deficiency may be observed in different brain structures, especially in the hippocampus (Costantini *et al*., 2008). Within the AD neuropathology, there is a shift in brain metabolism, which results in diminished cerebral glucose utilization (Yao *et al*., 2011). On the other hand, increased ketogenesis is observed during the aging process (Yao *et al*., 2011).

Mitochondrial dysfunction and oxidative stress play a significant role in neurodegeneration. Both processes are known to generate higher concentrations of ROS, which are harmful to all cellular macromolecules, including nucleic acid, lipid, and protein damage (Lauritzen *et al*., 2016).Therefore, KD may provide neuroprotective benefit by improving mitochondrial function through biochemical changes resulting from glycolysis inhibition and increased KBs formation (Figure 8). It is observed that metabolic ketosis may decrease ROS production improving mitochondrial respiration and bypassing complex 1 dysfunction (Cahill, 2006).

Moreover, KD modulates the ratio between the oxidized and reduced forms of nicotinamide adenine dinucleotide (NAD+/NADH). An increased NAD+/NADH ratio plays a role in protection against ROS and improves redox reactions, mitochondrial biogenesis, and cellular respiration, which stabilizes synaptic action (Bough *et al*., 2006; Yang and Sauve, 2016). A significant increase in the NAD+/NADH ratio was found in the brain cortex and hippocampus of KD-fed rats after two days (Elamin *et al*., 2017). After all, it induces the gene expression via sirtuin 1 (SIRT1), a type 3 histone deacetylase (Chen *et al*., 2017), involved in different processes related to deacetylating histone and non-histone targets (Pinto *et al*., 2018; North *et al*., 2003).

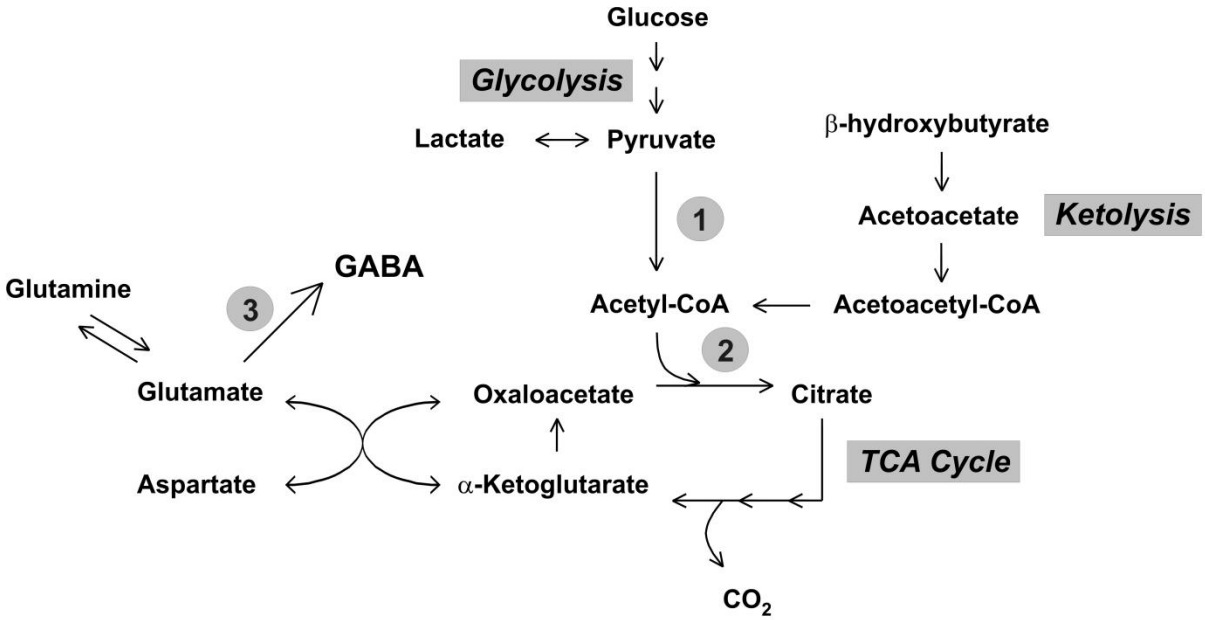

Figure 8: The metabolic inter-relationships between brain metabolism of glutamate, ketone bodies and glucose (Humana Press, Totowa, NJ, 2004).

In ketosis, 3-OH-butyrate (β-hydroxybutyrate) and acetoacetate contribute heavily to brain energy needs. A variable fraction of pyruvate (1) is ordinarily converted to acetyl-CoA via pyruvate dehydrogenase. In contrast, all ketone bodies generate acetyl-CoA which enters the tricarboxylic acid (TCA) cycle via the citrate synthetase pathway (2). This step involves the consumption of oxaloacetate, which is necessary for the transamination of glutamate to aspartate. Oxaloacetate is then less available as a reactant of the aspartate aminotransferase pathway, which couples the glutamate-aspartate interchange via transamination to the metabolism of glucose through the TCA cycle. Less glutamate is converted to aspartate, and thus more glutamate is available for synthesis of GABA (3) through glutamic acid decarboxylase (GAD). Adapted with permission from Yudkoff *et al*. The Ketogenic Diet: Interactions with Brain Amino Acid Handling, in Epilepsy and the Ketogenic Diet, Stafstrom CE & Rho JM (Eds), Humana Press, Totowa, NJ, 2004.

III.4 Parkinson Disease

Parkinson's disease is a progressive neurodegenerative disorder with an estimated prevalence of 0.3 percent in the U.S. population (de Lau LM *et al*., 2004). The prevalence increases to 4 to 5 percent in those older than 85 years (de Lau LM *et al*., 2004). Characteristic neuropathologic features of the disease are dopaminergic neuron degeneration in the substantia nigra and the presence of eosinophilic intracytoplasmic inclusions (Lewy bodies) in the residual dopaminergic neurons (Nutt JG and Wooten GF, 2005).

The clinical presentation of Parkinson's disease is similar to that of diverse neurologic disorders called parkinsonisms (Italian Neurological Society, 2003; Seritan *et al*., 2004). Symptoms that suggest a diagnosis other than Parkinson's disease include lack of response to levodopa, hallucinations, prominent and early dementia, early postural instability, severe and early autonomic dysfunction, upward gaze paralysis, and involuntary movements other than tremor (Italian Neurological Society, 2003).

III.4.1 Etiopathogenesis of Parkinson's disease

The relative contribution of genes and environmental/lifestyle factors in pathogenesis of PD has been debated. With median age at onset at 60 years, age is the single most important risk factor for PD (Ascherio and Schwarzschild, 2016; Simon *et al*., 2020). The frequency appears higher in men compared with women (ratio ranges from 1.3 to 2.0) but the incidence may be influenced by differences in prevalence of variables such as cigarette smoking behaviour, use of postmenopausal hormones and caffeine intake (see section on lifestyle and protective factors) (Ascherio and Schwarzschild, 2016). Like in other neurodegenerative diseases, age-related biological dysfunction including telomere dysfunction, genomic instability, epigenetic changes, ubiquitin-proteasome and autophagylysosomal system, and mitochondrial defects, may underpin and facilitate neuronal demise (González-Casacuberta *et al*., 2019;Pohl and Dikic, 2019).

Subtypes of PD have been proposed, categorising patients according to distinct clinical clusters, such as tremor-dominant and postural-instability-gait-disorder (PIGD) subtypes (Thenganatt and Jankovic, 2014; Prange *et al*., 2019). Many studies have found that the PIGD phenotype is characterised by more severe disease manifestation and more rapid progression than the tremor-dominant for of PD. It has been suggested the clinical subtypes both determine the phenotype and natural progression/prognosis and also reflect underlying and distinct pathogenic mechanisms. This concept, however, has been challenged because motor subtypes are not fixed but change with progression of the disease and with treatment (Mestre *et al*., 2018; De Pablo-Fernández *et al*., 2019; Luo *et al*., 2019).

III.4.2 The Ketogenic Diet and Parkinson's disease

In Parkinson's disease (PD), dopaminergic neurons in the substantia nigra are affected by a degeneration process leading to motor and non-motor disturbances. Animal and in vitro studies have demonstrated a beneficial effect of ketone bodies on the course of PD.

1-methyl-4-phenyl-1,2,3,6-tetrahydropyridine (MPTP) produced the death of dopaminergic substantia nigral cells, both in vitro and in vivo, producing a syndrome indistinguishable from Parkinson's disease. It was shown that beta-hydroxybutyrate acts in vitro as a neuroprotective agent against the toxicity of MPTP on dopaminergic neurons (Kashiwaya *et al*., 2000). In addition, Tieu *et al*. (Tieu *et al*., 2003) concluded that in mice administered with the MPTP neurotoxin, which induces a defect of the mitochondrial complex I, an administration of beta-hydroxylactate reduced the neurotoxicity of the compound via effects exerted on complex II and by improvement of cellular respiration and ATP production. Improved motor skills were also seen in the experimental mice, together with an increased dopamine volume in the mesencephalon. Shaafi *et al*. (Shaafi *et al*., 2016) observed in a rat model of Parkinson's diseases a beneficial influence of the KD on the motor function of the experimental animals. Moreover, a combination of the diet with pramipexole increased the efficacy of the medicinal product. Joniec-Maciejak *et al*. (Joniec-Maciejak *et al*., 2018) examined the possible protective effects of octanoic acid in the mouse model of PD induced by MPTP. They observed that the administration of octanoic acid led to inhibition of the neurodegenerative processes seen after MPTP administration. The results suggested that a probable mechanism of the neuroprotective action of octanoic acid is related to an increase in metabolic activity in striatal mitochondria. In vitro studies also revealed a potentially advantageous influence of ketone bodies on the functionality of synapses in an induced dysfunction of the respiratory mitochondrial chain, caused by an administration of rotenone, being an inhibitor of complex I and of the 3-nitropropionic acid, which is an inhibitor of complex II. The protective effects of ketone bodies could result from an antioxidative activity (Figure 3), improved ATP synthesis, and from the effect on the ATP-sensitive potassiumchannel (K_{ATP}) (Kim *et al*., 2010; Kim *et al*., 2015). In other studies, the beneficial effects of ketone bodies were described, resulting from a mitigated inflammatory condition induced by MPTP administration (Yang X and Cheng B, 2010) and from reduced apoptosis of dopaminergic cells exposed to substances causing their death (Cheng B *et al*., 2007). In a study on a rat model of Parkinson's disease, Cheng *et al*. (Cheng B *et al*., 2009) concluded that KD, via glutathione activity, exerted a neuroprotective effect against the toxic effect of 6-hydroxydopamine (Dariusz Włodarek, 2019).

In a clinical study, Vanitallie *et al* (Vanitallie *et al*., 2005). observed 5 patients with PD who had agreed to adhere to KD rules in their home environments. The observation continued for 28 days. The researchers observed some improvement in the scores of the Unified Parkinson's Disease Rating Scale (UPDRS), while not excluding the possibility of placebo effects. It is worth emphasizing that in the KD applied in the study, the contribution of particular components to the energetic value of the diet was 90% for fat, 2% for carbohydrates, and 8% for protein. In a habitual diet, the proportion of energy from proteins is higher, while a low-protein diet improves the bioavailability of levodopa. Four of the studied patients received levodopa. Therefore, when evaluating the effects of KD on improved UPDRS scores in their respective cases, one should also take into account the possible effect of protein supply. Very interesting data came from the research of Phillips *et al*. on this topic (Phillips *et al*., 2018). They assessed the effect of a low-fat versus ketogenic diet in 47 patients with Parkinson's disease (38 individuals completed the study). The low–fat diet provided 1750 kcal per day, composed of 42 g of fat (approximately 22% of energy), 75 g of proteins (17% of energy), 246g of carbohydrates (56% of energy), and 33 g of fiber (5%). The ketogenic diet provides 1750 kcal per day, composed of 152 g of fat (approximately 78% of energy), 75 g of protein (17% of energy), 16g of carbohydrates (3–5% of energy), and 11 g of fiber (1–5% energy). For those with higher energy needs, a calorie-booster was prepared with an adequate diet proportion of macronutrients. The diets were followed for eight weeks. Both diet groups showed significantly improved motor and non-motor symptoms; however, the ketogenic group showed greater improvements in non-motor symptoms (Dariusz Włodarek, 2019).

III.5Type 2 diabetes

Diabetes mellitus (DM) is a group of metabolic disorders characterized by a chronic hyperglycemic condition resulting from defects in insulin secretion, insulin action or both. Permanent neonatal diabetes is caused by glucokinase deficiency, and is an inborn error of the glucose-insulin signaling pathway (Njolstad *et al*., 2003). The prevalence of diabetes is increasing rapidly worldwide and the World Health Organization (2003) has predicted that by 2030 the number of adults with diabetes would have almost doubled worldwide, from 177 million in 2000 to 370 million. Experts project that the incidence of diabetes is set to soar by 64% by 2025, meaning that a staggering 53,1 million citizens will be affected by the disease (Rowley and Bezold, 2012).

There are primarily two types of diabetes. Type 1 diabetes is an autoimmune disease in which the pancreas can no longer produce insulin. As a result, the body cannot control blood sugar levels. The key characteristics of type 1 diabetes are its onset mostly in young people and

the extremely wide global variation in the incidence of the disease. There is a comprehensive lack of knowledge about the cause of this disease, (Shaw *et al*., 2010) and it remains an epidemiological puzzle. The overall standardized incidence varies from 0.1:100 000 per year in the Zunyi region of China to more than 40:100 000 per year in Finland (Shaw *et al*., 2010). Type 1 diabetes appears to be on the increase in almost all populations. In Europe, the incidence of (childhood onset) type 1 diabetes continues to rise but the increase is not necessarily uniform. This pattern of change suggests that key risk exposures differ over time in different European countries (Patterson CC *et al*., 2012).

Type 2 diabetes (previously called adult onset) is a metabolic disorder in which the body gradually becomes insensitive to the action of insulin with decreased beta cell mass and progressive beta cell failure so that blood sugar control is also compromised. Overall, the prevalence of type 2 diabetes dominates the total diabetes burden. In developed countries, most people with diabetes are aged over 60 years, while in developing countries the disease mainly affects people of working age (40 to 60 years) (World Health Organization, 2008).

III.5.1 Etiopathogenesis of type 2 diabetes's disease

Type 2 diabetes is a heterogenous disorder caused by a combination of genetic factors related to impaired insulin secretion, insulin resistance and environmental factors such as obesity, over eating, lack of exercise, and stress as well as aging (Kaku, 2010). It is typically a multifactorial disease involving multiple genes and environmental factors to varying extents (Holt, 2004).

Under normal physiological conditions, plasma glucose concentrations are maintained within a narrow range, despite wide fluctuations in supply and demand, through a tightly regulated and dynamic interaction between tissue sensitivity to insulin (especially in liver) and insulin secretion (DeFronzo, 1988). In type 2 diabetes, these mechanisms break down, with the consequence that the two main pathological defects in type 2 diabetes are impaired insulin secretion through a dysfunction of the pancreatic β-cell, and impaired insulin action through insulin resistance (Holt, 2004).

Obesity has genetic as well as environmental causes. It has a strong effect on the development of type 2 DM (Bjorntorp, 1992; Haffner *et al*., 1992) as it is found in Western countries (NDDG, 1979; Wilson *et al*., 1981) and some ethnic groups such as Pima Indians (Joffe *et al*., 1992; Knowler *et al*., 1993). Obesity is more than just a risk factor; it has a causal effect in the development of type 2 DM against a genetic background. The evolution from obesity to type DM results from a succession of pathophysiological events:

(a) Augmentation of the adipose tissue mass, leading to increased lipid oxidation;

(b) Insulin resistance noted early in obesity, revealed by euglycemic clamp, as a resistance to insulin mediated glucose storage and oxidation, blocking the function of the glycogen cycle;
(c) Despite maintained insulin secretion, unused glycogen prevents further glucose storage leading to type 2 DM;
(d) Complete b-cell exhaustion appears later (Felber, 1992).

III.5.2 The Ketogenic Diet and type 2 diabetes's disease

For decades, the pathogenesis of obesity has been explained as calories introduced in amounts exceeding energy expenditure (Schwartz *et al*., 2017). More recently, the scientific discussion on the pathogenesis of obesity has focused on the question: "Is a calorie a calorie?" in other words, whether the consumption of different types of food predisposes to weight gain independently of the number of calories consumed. According to a recent Endocrine Society statement (Schwartz *et al*., 2017), the answer to that question is "yes", i.e., when calorie intake is held constant, body weight is not affected by changes in the amount and type of nutrients in the diet. However, it is known that the type of food impacts on the number of calories consumed, for example diets high in simple sugars and processed carbohydrates are usually high in calories and low in satiety-promoting fiber and other nutrients, favoring an increase in overall energy intake (Schwartz *et al*., 2017).

Some researchers (Ludwig and Ebbeling, 2018) point out that the conventional model of obesity does not explain the obesity and metabolic diseases epidemic of the modern era. In a study by Leibel *et al*. (Leibel *et al*., 1995), maintenance of a reduced or elevated body weight was associated with compensatory changes in energy expenditure and hunger, with the former declining while the latter has been increasing. These compensatory changes may account for the poor long-term efficacy of treatments for obesity, and understanding this physiological adaptation is of practical importance in order to approach the current obesity epidemic (Andrea Mario Bolla *et al*., 2019).

According to an alternative view, dietary components have a main role in producing hormonal responses that cause obesity, and certain types of carbohydrate can alter the homeostatic mechanism that limits weight loss (Ludwig and Ebbeling, 2018). The carbohydrate-insulin model (CIM) of obesity hypothesizes that a high-carbohydrate/low-fat diet causes postprandial hyperinsulinemia that promotes fat deposition and decreases circulating metabolic fuels (glucose and lipids), thereby increasing hunger and slowing the whole-body metabolic rate. In this view, overeating is a consequence of increasing adiposity, rather than the primary cause. Insulin is the most potent anabolic hormone that promotes glucose uptake into tissues, suppresses release of fatty acid from adipose tissue, inhibits

production of ketones from liver and stimulates fat and glycogen deposition. Dietary carbohydrates are the main driving force for insulin secretion and are heterogeneous in their glycemic index (GI) (an index of how fast blood glucose rises after their ingestion) (Ludwig, 2018), and glycemic load (GL) (derived from carbohydrate amount and glycemic index). The latter is the best predictor of post prandial blood glucose levels after CHO ingestion (Wolever and Bolognesi, 1996). As carbohydrates are the main source of glucose, reducing their intake may lead to a decrease in insulin requirements, an improvement in insulin sensitivity and a reduction of post-prandial glycaemia (Accurso *et al*., 2008). In these terms, LCD may have a positive effect in the management of metabolic diseases and in the pathogenesis of obesity (Andrea Mario Bolla *et al*., 2019).

III.6 Cancer

Cancer is a group of diseases involving abnormal cell growth with the potential to invade or spread to other parts of the body (World Health Organization, 2018; National Cancer Institute, 2007). These contrast with benign tumors, which do not spread (National Cancer Institute, 2007). Possible signs and symptoms include a lump, abnormal bleeding, prolonged cough, unexplained weight loss, and a change in bowel movements (NHS Choices, 2014). While these symptoms may indicate cancer, they can also have other causes (NHS Choices, 2014). Over 100 types of cancers affect humans (National Cancer Institute, 2007).

Cancer is amongst the top three causes of death in the developed world, both in the US and in Puerto Rico. In 2014, 591,699 people died of malignant tumors in the US, only 25,000 (US Department of Health and Human Services, 2016) and in 2012 cancer killed more people in Puerto Rico than heart disease, averaging 5,439 people per 100 thousand inhabitants; to 5,089 for heart disease (Departamento de Salud De Puerto Rico, 2014). Even though earlier detection of cancer has progressed the amount of deaths per year of cancer has barely changed in the last 50 years, while improvement in the treatment of Heart Disease has been significant, thus closing the gap between these 2 main killers (Heron and Anderson, 2016). This could be considered a treatment setback, due to lack of progress against this degenerative disease, as the standard of care seems in the need of new and effective treatment options to improve the prognosis against cancer. For this reason, recent studies have been directed into the metabolic aspects of cancer. The idea of treating cancer as a metabolic disease instead of a genetic one is appealing. This is due to the fact that research has not been able to find a specific genetic cause, but has found at least seven metabolic differences between cancerous and normal healthy cells (Gonzalez *et al*., 2012):

1. A shift from respiratory (aerobic) pathways as a main ATP production mechanism to fermentative (anaerobic) pathways (Oxidative phosphorylation to Fermentation).

2. Mitochondrial dysfunction; both in structure and function, as mitochondria lose their cristae and membrane potential, thus diminishing their energy production potential. Creating what has been named as ghost mitochondria.
3. Increased glycolysis, which raises lactic acid production thus lowering pH levels and oxygen transport efficiency.
4. Formation of coagulated proteins around cancerous cells, which shield these from the host immunological response (Cellular and humoral).
5. Augmented and uncontrolled cellular replication.
6. Loss of communication between cells.
7. Metastasis or colonization of other tissues by transformed cells.

III.6.1 The Ketogenic Diet and cancer

Cancer has recently been regarded as a metabolic disease, and studies have started to examine metabolic therapy using a ketogenic diets as a complementary or alternative therapy for cancer (Seyfried *et al*., 2014). The ketogenic diet is a low-carbohydrate, high-fat diet designed to increase the blood concentration of ketone bodies as an alternative source of energy to glucose (Allen *et al*., 2014). When humans experience insufficient glucose supply because of fasting or long-term exercise, they metabolize fat and generate ketone bodies (β-hydroxybutyrate and acetoacetate) from fatty acids as sources of energy (Vidali *et al*., 2015). The ketogenic diet has been prescribed since the 1920s to treat refractory epileptic seizures in children (Gasior *et al*., 2006). As the ketogenic diet switches the energy source for cells from glucose to fatty acids and ketone bodies, it is also used for the dietary management of specific metabolic disorders such as glucose transporter 1 (GLUT1) deficiency and pyruvate dehydrogenase complex deficiency (Vidali *et al*., 2015). In Japan, a special infant formula with a high-fat, low-carbohydrate composition, which is formulated with medium chain triglycerides (MCTs) with a ketogenic ratio of 3:1, has long been used for ketogenic dietary therapy for infants with congenital metabolic disorders and refractory epilepsy (Hayashi *et al*., 2013).

In most cancer cells, oxidative phosphorylation in the mitochondria is inadequate, even in the presence of oxygen, and energy from anaerobic glycolysis is enhanced to compensate for this (the Warburg effect) (Seyfried and Shelton, 2010). Cancer cells thus require large amounts of glucose. As cancer cell mitochondria are dysfunctional, they cannot readily use fatty acids and ketone bodies, which can be used as energy sources by healthy cells (Seyfried and Shelton,

2010). The Warburg effect is the target of ketogenic dietary therapy for cancer, as such diets aim to limit energy sources for cancer cells by restricting carbohydrates, while providing fatty acids and ketone bodies as an energy source for healthy cells (Seyfried *et al*., 2014).

III.6.1.1 Ketogenic diet targets glucose metabolism of cancer cells

Most solid cancers share metabolic features such as increased glucose uptake and reliance on glycolysis. In the Warburg effect, cancer cells predominantly use glycolysis for energy production accompanied by the production of lactate, paradoxically even if sufficient oxygen for respiration is present (Hay, 2016). Therefore, it could be hypothesized that the Warburg effect in cancer cells could be at least partially targeted by creating chronic metabolic stress due to low glucose supply provoked by dietary intervention with a KD and/or calorie restriction. Numerous preclinical studies on different types of cancer demonstrate that the KD, particularly in combination with calorie restriction, reduces circulating blood glucose levels. The reduction in glucose levels is accompanied by a reduction of insulin and/or IGF levels in the blood (Hopkins, 2018; Urbain *et al*., 2017; Seyfried *et al*., 2003). The activation of insulin and/or IGF receptor signaling pathways contributes to tumorigenesis (Bowers *et al*., 2015). In this context, a study including 9778 patients identified hyperinsulinemia as a risk factor in cancer prognosis (Tsujimoto *et al*., 2017). Clinical studies have demonstrated a reverse correlation between the level of ketosis and the levels of glucose, insulin and/or IGF-1 (Fine *et al*., 2012; Cohen *et al*., 2018; Fraser *et al*., 2000).The insulin-activated enzyme PI3K frequently exhibits enhanced activity in different types of cancer, due to PI3K gene mutations. Thus, PI3K inhibitors are considered as potent anticancer drugs. However, clinical trials have shown that targeted PI3K drugs often cause hyperglycemia (Janku, 2017), leading to increased insulin levels and reactivation of the PI3K pathway, which ultimately results in treatment resistance. Recently, it was shown that the KD improved the efficacy of anti-PI3Ktreatment and drug resistance by limiting the acute glucose-insulin feedback induced by PI3K inhibitors, thus blocking this loop (Hopkins *et al*., 2018). In most cancer cells, accumulation of lactic acid, the major product of aerobic glycolysis, is detected (Jiang, 2017). It was shown that after three days of a KD, the level of lactic acid was diminished in the tumor tissue of patients with head and neck cancer (Schroeder *et al*., 2013). In addition, reduction of another prognostic aerobic glycolysis-related marker, transketolaselike-1, was reported in patients who strictly used the KD (Jansen and Walach, 2016).Taken together, reduction of blood glucose seems to be a contributing factor in the effectiveness of the KD against cancer growth. Some preclinical studies showed that ad libitum KD, which failed to reduce the blood glucose level, was not able to reduce tumor growth (Morscher *et al*., 2016; Maurer *et al*., 2011; Stemmer *et al*., 2015), while additional calorie

restriction or increasing the KD ratio led to both significant blood glucose reduction and tumor growth suppression (Morscher *et al*., 2016; Zhou *et al*., 2007 ; Stemmer *et al*., 2015). Interestingly, in two preclinical studies, medulloblastoma and glioma did not respond to KD therapy, even though the KD (4:1) significantly reduced blood glucose (De Feyter *et al*., 2016; Dang *et al*., 2015) and insulin levels (Dang *et al*., 2015).

III.6.1.2 Ketogenic diet targets mitochondrial metabolism of cancer cells

Some tumor entities are not able to properly respire due to a dysfunctional OXPHOS system. The mode of downregulation of OXPHOS can differ in different types of cancer. Thus, some tumors show a reduction of mitochondrial mass, others a reduction of all OXPHOS complexes and some, such as paragangliomas and oncocytictumors, have pathogenic mutations in OXPHOS genes (Astuti *et al*., 2001;Simonnet *et al*., 2003).Tumors with dysfunctional mitochondria or decreased mitochondrial activity seem to compensate their energy requirements by aerobic fermentation (Meidenbauer *et al*., 2015). Replacing glucose by ketone bodies requires that the tumors have functional mitochondria to be able to use ketone bodies efficiently for growth and survival. Thus, tumors with dysfunctional or low levels of mitochondria might suffer from high metabolic energy stress triggered by a KD (Aminzadeh-Gohari *et al*., 2017; Martuscello *et al*., 2016; Meidenbauer *et al*., 2015; Seyfried *et al*., 2011). Analysis of the cellular energy sensor AMP-activated protein kinase (AMPK) in neuroblastoma tumors revealed that the KD increased the levels of activated AMPK (Aminzadeh-Gohari *et al*., 2017).

On the other hand, tumor mitochondria can possess high activity in terms of respiration and energy production (Gogvadze *et al*., 2010; Feichtinger *et al*., 2017). The question is whether the KD may also target tumors that have functional mitochondria. Rapidly growing tumors develop hypoxic areas in which oxygen supply is sparse (Gogvadze *et al*., 2010). Due to the capability of tumor cells to metabolize ketone bodies solely if enough oxygen is available (Otto *et al*., 2014), tumor cells at hypoxic sites would fail to produce energy from ketone bodies even though these cells have functional mitochondria. The three mitochondrial enzymes SCOT, BDH1, and ACAT1 are key players in ketone body utilization. Thus, therapeutic efficacy might be influenced by the expression of these enzymes. For example, neuroblastoma and pancreatic cell lines and mouse xenografts with very low or no SCOT expression can be targeted by ketone bodies and KD (Zhang *et al*., 2018; Morscher *et al*., 2015; Skinner *et al*., 2009). In a recent clinical trial, differential expression of ketolytic enzymes (including BDH1 and OXCT1) was described in gliomas. The authors hypothesized that patients with low or very low expression of BDH1 and OXCT1 in malignant gliomas may respond better to KD therapy than patients

with gliomas that express higher levels of ketolytic enzymes (Chang *et al* 2013; Zhang *et al*., 2018). In contrast, it has been shown that cancer cells of different origin can indeed take up and metabolize ketone bodies (Huang *et al*., 2016; Shakery *et al*., 2018). In vitro analyses of several different breast cancer cell lines revealed that physiologic concentrations of ketone bodies did not reduce cell proliferation independent of the expression level of ketolytic enzymes (Bartmann *et al*., 2018). Moreover, in a rat model of glioma, where the tumor cells were competent in the transport and oxidation of ketone bodies, a KD had no effect on cancer growth (De Feyter *et al*., 2016). Taken together, it is still unclear whether ketone bodies play a major causal role in the antitumor effect of KDs.

III.6.1.3 Ketogenic diet targets amino acid metabolism of cancer cells

Based on the results of several animal model studies, the KD alters amino acid (AA) metabolism and urea cycle metabolites (Aminzadeh-Gohari *et al*., 2017; De Feyte *et al*., 2016; Yudkoff *et al*., 2007; Roberts *et al*., 2016). The most consistent and pronounced changes observed were decreased blood levels of most essential AAs in mouse or rat(Aminzadeh-Gohari *et al*., 2017; Douris *et al*., 2015 ; Roberts *et al*., 2016). In addition, in different studies, alterations of metabolism of other AAs such as glutamate/glutamine, glycine, serine, proline, tryptophan, and aspartate were reported (Aminzadeh-Gohari *et al*., 2017; De Feyte *et al*., 2016; Yudkoff *et al*., 2007; Roberts *et al*., 2016). Douris *et al*. concluded that the KD led to down-regulation of AA catabolic processes in mice to conserve AA levels (Douris *et al*., 2015).

In a preclinical neuroblastoma model, reductions of essential AAs and urea cycle metabolites in plasma and tumors were induced by low protein KDs, whereas the plasma levels of serine, glycine and glutamine were elevated (Aminzadeh-Gohari *et al*., 2017). Mouse models of glioma administered a KD also showed higher levels of glutamate in the cortex and tumor tissue (De Feyte *et al*., 2016). In agreement, a clinical study reported increased levels of glutamine and/or glutamate in some patients with brain tumors after administration of a KD (Artzi *et al*., 2017). Considering the dependence of a range of tumor cells on glutamine and glutamate metabolism, it is surprising that the observed elevated levels of these AAs did not trigger tumor proliferation. The impact of the KD on down-regulation of essential AAs most likely contributes to the inhibition of tumor growth, but this needs further investigation. It can be postulated that the reduction of essential AAs might result from relatively low amounts of protein in the KD. In contrast, Aminzadeh-Gohari *et al*. found neither a reduction of plasma essential AAs nor a reduction in tumor growth in mice fed a control diet containing the same low amount of protein as the KD (Aminzadeh-Gohari *et al*., 2017).

III.7 Other medical and therapeutic applications of ketogenic diet

III.7.1 Ketogenic Diet and Motor Function

III.7.1.1 Protective effects of KD on the neuromuscular system

The effects of KD administration on the neuromuscular system come through different mechanisms. For one, KD can directly induce metabolic shifts due to the high blood levels of KBs and to the restriction of carbohydrate intake (Danial *et al*., 2013). KD can also modify nutrient-integrating pathways, such as the mTOR pathway, involved in autophagy and mitophagy-related mitochondrial renewal. Finally, KD might have potential, indirect roles, such as effects on neurotransmission, oxidative stress, and inflammatory mechanisms. Figure 9 sums up the cellular mechanisms induced by KD.

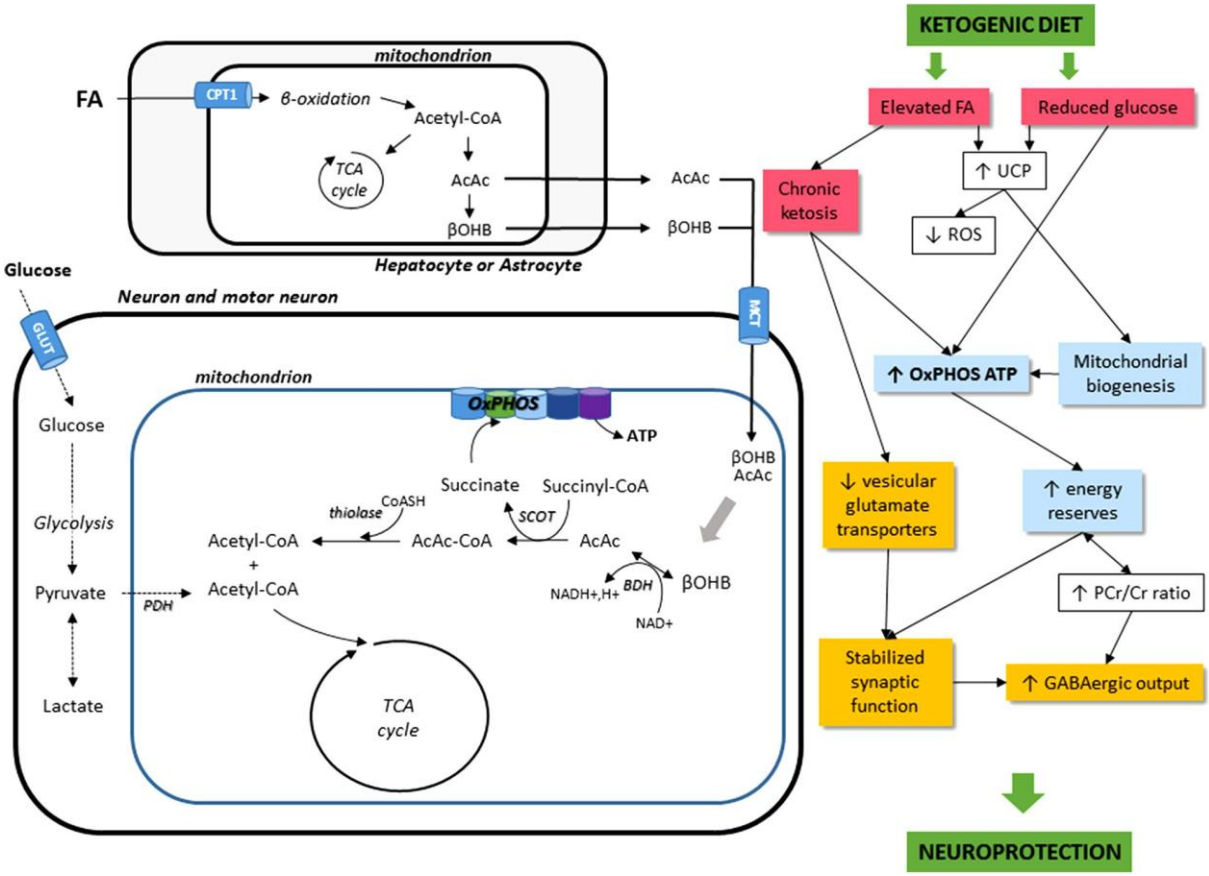

Figure 9: Illustration of the main cellular mechanism in the KD on the neuromuscular system (Charlotte Veyrat-Durebex *et al*., 2018)

III.7.1.1.1 Metabolism Switch

Ketogenic diet has a high impact in tissues with a highenergy requirement and with challenges from modifications in metabolic substrates, such as the neuromuscular system.

The brain represents 2% of one's body weight but consumes about 20% of the body's energy stores (Belanger *et al*., 2011) in order to fuel the processes of neurotransmitter

production/recycling, vesicular trafficking, maintenance of ion gradients for the propagation of action potentials, and memory, to name a few. Similarly, in the resting state, 20% of the energy expenditure is devoted to muscle (Gallagher *et al*., 1998), and it can largely increase with muscle contractions, for example for transforming organelles, enzymatic activities, intracellular signaling, and transcriptional responses (Coffey *et al*., 2007).

Ketogenic diet promotes KBs (acetoacetate and b-hydroxybutyrate) production in the liver from acetyl-CoA formed during mitochondrial b-oxidation of fatty acids. Some of the acetyl-CoA enters the TCA cycle, and the excess is used to form acetoacetate, which could be converted to bOHB by bOHB dehydrogenase (BDH) enzyme or spontaneously converted to acetone (Newman and Verdin, 2014). KBs are transported to other tissues (brain, muscle, and heart) through the blood and used as fuel, especially in the brain (Kunnecke *et al*., 1993; Rae *et al*., 2012; Achanta and Rae, 2017). It has also been reported that astrocytes can produce KBs from fatty acids (Auestad *et al*., 1991) and leucine (Bixel and Hamprecht, 1995). Astrocytes present the same preference for fatty acids (rather than glucose) as metabolic fuel and have enzymatic machinery similar to that of cultured hepatocytes (Guzman and Blazquez, 2001).

III.7.1.1.2 Synaptic Transmission

Numerous reports have suggested that the anticonvulsive mechanisms behind ketosis are based on a metabolic shift between the neurotransmitters GABA and glutamate, resulting in an increased inhibition and/or decreased excitation (Bough and Rho, 2007; Yudkoff *et al*., 2007). This could spark attention toward neuromuscular transmission (Diana *et al*., 2017). Indeed, KD can induce an increase in glutamate decarboxylase expression in the striatum of rats (Cheng *et al*., 2004) and an alteration of astrocytic GABA degradation via a modification of GABA transaminase activity (Suzuki *et al*., 2009). Moreover, GABA content is increased by KBs in rat brain synaptosomes (Erecinska *et al*., 1996), rat hippocampus (Calderon *et al*., 2017), and in the brain of patients (Wang *et al*., 2003). Some authors havereported the inhibition of glutamatergic, synaptic transmission (Danial *et al*., 2013; Lutas and Yellen, 2013), which implies a blockade of vesicular glutamate transporters (Juge *et al*., 2010). This interference with glutamate-mediated toxicity, implied in neuronal injury, could explain the interest for KD in neurological diseases.

III.7.1.1.3 Signaling Pathways

Ketogenic diet could modulate crucial mechanisms in cellular homeostasis. For example, mTOR and AMPK pathways involved in cell proliferation, energetic metabolism, or protein biosynthesis could be implicated. KD induces the binding of insulin and free IGF-1 to their specific tyrosine kinase receptors and activates the phosphatidylinositol-3 kinase (PI3K)-

Akt-mammalian target of rapamycin complex 1 (mTORC1). However, this effect is counteracted by the decrease in the intracellular ATP/AMP ratio and the activation of liver kinase B1 (LKB1)-AMP-activated protein kinase (AMPK) signaling, inhibiting mTORC1 (Newman and Verdin, 2014). Such effects may be essential for motor dysfunction in ALS, for example, as deregulation in mTOR and AMPK signaling pathways has been described in this disease (Saxena *et al*., 2013; Perera and Turner, 2016).

III.7.1.2 Use of KD in motor dysfunction

The beneficial effect of KD has been hypothesized in various diseases, such as epilepsy, metabolic defects, cancers, autism, depression, migraines, narcolepsy, Parkinson's disease, and Alzheimer's disease (Vanitallie *et al*., 2005; Baranano and Hartman, 2008; Newport *et al*., 2015).

III.7.1.2.1Amyotrophic Lateral Sclerosis (ALS)

Amyotrophic lateral sclerosis is a fatal, neurodegenerative condition characterized by motor neuron degeneration that leads to progressive motor weakness and death between 2 and 5 years from onset (Korner *et al*., 2013). Many molecular mechanisms have been involved in ALS pathophysiology, but the starting point of the disease remains unclear. Drug development has yielded few successes, and the prognosis has not changed dramatically since the first reports, nearly 150 years ago. Regarding studies on ALS mouse models, (Siva, 2006) proposed KD as a promising strategy to slow down the progression of ALS, especially through the increase in mitochondrial function. The main mechanisms related to mitochondrial malfunction and ALS have been recently reviewed (Carri *et al*., 2017). Mitochondrial dysfunction may cause motor neuron death by predisposing them to calcium-mediated excitotoxicity, by increasing generation of reactive oxygen species, and by initiating the intrinsic apoptotic pathway (Giovanni Manfredi and Zuoshang Xu, 2017).

III.7.1.2.2 Angelman Syndrome (AS)

Angelman syndrome is a devastating, neurological disorder with no treatment. AS patients suffer from motor dysfunction, intellectual disability, frequent smiling and laughter, lack of speech, and severe seizures. This syndrome is due to an alteration in the E3 ubiquitin ligase (Margolis *et al*., 2015). The main pathophysiological pathways concern an impairment in synaptic plasticity, deregulated dopaminergic and GABAergic neurons, abnormal mTOR signaling in the cerebellum, abnormal cell contact signaling and excitation/inhibition imbalance (Bi *et al*., 2016). It has been shown, as well, that the stimulation of mitochondrial biogenesis by KD improves the hippocampal deficits in AS mice (Bough *et al*., 2006; Su *et al*., 2011).

III.7.1.2.3 Mitochondrial Myopathy

Mitochondrial disorders are clinically and genetically heterogeneous diseases with a neuromuscular component caused by mutations either in mitochondrial DNA or in nuclear genes encoding mitochondrial proteins. Interestingly, KD has showed a relevant effect on a mouse model for late-onset mitochondrial myopathy characterized by generalized muscle weakness (Ahola-Erkkila *et al*., 2010). KD decreased the amount of Cytochrome c Oxidase-negative muscle fibers and protected mitochondrial ultrastructure in the muscle. A recent study suggested that the use of KD in mitochondrial myopathy enhanced muscle strength and delayed the progression of the disease but might induce muscle damage in a subpopulation (Ahola *et al*., 2016).

III.7.2 The Ketogenic Diet and Dermatology

III.7.2.1 NLRP3 Inflammasome Suppression

The NLRP3 inflammasome serves as the activating platform for IL-1β. (Youm YH *et al*., 2015) Aberrant and elevated IL-1β levels cause or are associated with a number of dermatologic diseases namely, the auto inflammatory syndromes, hyperimmunoglobulinemia D with periodic fever syndrome, tumor necrosis factor–receptor associated periodic syndrome, juvenile idiopathic arthritis, relapsing polychondritis, Schnitzler syndrome, Sweet syndrome, Behçet disease, gout, sunburn and contact hypersensitivity, hidradenitis suppurativa, and metastatic melanoma. (Fomin D *et al*., 2017) Clearly, the ketogenic diet may be employed in a therapeutic manner (though to what degree, we need further study) for these dermatologic conditions based on the interaction with the NRLP3 inflammasome and IL-1β.

III.7.2.2 Acne

A link between acne and diet has long been suspected, but a lack of well-controlled studies has caused only speculation to remain. Recent literature suggests that the effects of insulin may be a notable driver of acne through effects on sex hormones and subsequent effects on sebum production and inflammation. Cordain *et al* (2002) discuss the mechanism by which insulin can worsen acne in a valuable article, which Paoli *et al* (Paoli *et al*., 2012) later corroborated. A ketogenic diet could help ameliorate acne because it results in very little insulin secretion, unlike the typical Western diet, which causes frequent large spikes in insulin levels. Furthermore, the anti-inflammatory effects of ketones would benefit the inflammatory nature of this disease.

III.7.2.3 DM and Diabetic Skin Disease

Diabetes mellitus carries with it the risk for skin diseases specific to the diabetic disease process, such as increased risk for bacterial and fungal infections, venous stasis, pruritus (secondary to poor circulation), acanthosis nigricans, diabetic dermopathy, necrobiosis lipoidica diabeticorum, digital sclerosis, and bullosis diabeticorum (American Diabetes Association, 2019). It is well established that better control of DM results in better disease state outcomes (Greenapple R, 2011). The ketogenic diet has shown itself to be a formidable and successful treatment in the diseases of carbohydrate intolerance (eg, metabolic syndrome, insulin resistance, type 2 DM) because of several known mechanisms, including less glucose entering the body and thus less fat deposition, end-product glycation, and free-radical production (discussed below); enhanced fat loss and metabolic efficiency; increased insulin sensitivity; and decreased inflammation (Paoli A *et al*., 2013). Lowering a patient's insulin resistance through a ketogenic diet may help prevent or treat diabetic skin disease.

III.7.2.4 Dermatologic Malignancy

A ketogenic diet has been of interest in oncology research as an adjunctive therapy for several reasons: anti-inflammatory effects, anti-oxidation effects, possible effects on mammalian target of rapamycin (mTOR) regulation, (Fomin D *et al*., 2017) and exploitation of the Warburg effect (Allen BG *et al*., 2014). One article discusses how mTOR, a cell-cycle regulator of particular importance in cancer biology, can be influenced by ketones both directly and indirectly through modulating the inflammatory response (Fomin D *et al*., 2017). There are several small studies of the effects of ketogenic diets on malignancy, and although none of these studies are of substantial size or control, they show that a ketogenic diet can halt or even reverse tumor growth (Zhou W *et al*., 2007).

III.7.2.5 Oxidative Stress

Oxidative stress, a state brought about when reactive oxygen species (ROS) production exceeds the antioxidant capacity of the cell and causes damage, is known to be a central part of certain skin diseases (eg, acne, psoriasis, cutaneous malignancy, varicose ulcers, cutaneous allergic reactions, and drug-induced skin photosensitivity) (Fomin D *et al*., 2017). There are 2 proven mechanisms by which a ketogenic diet can augment the body's innate anti-oxidation capacity. First, ketones activate a potent antioxidant upregulating protein known as NRF2, which is bound in cytosol and remains inactive until activated by certain stimuli (ie, ketones) (Venugopal Rand Jaiswal, 1996). Second, a ketogenic diet results in fewer produced ROS and

an increase in the nicotinamide adenine dinucleotide ratio produced by the mitochondria; in short, it is a more efficient way of producing cellular energy while enhancing mitochondrial function. When fewer ROS are produced, there is less oxidative stress that needs to be attended to by the cell and less cellular damage. Feichtinger *et al* point out that mitochondrial inefficiency and dysfunction often are overlooked components in several skin diseases, and based on the studies discussed above, these diseases may be aided with a ketogenic diet (Feichtinger *et al*., 2014).

III.7.3 Effects of ketogenic diet and ketone bodies on the cardiovascular system:

III.7.3.1 Detrimental vascular effects of high ketone bodies and BHB concentrations in diabetic ketoacidosis

The morbidity and mortality burden of type 1 diabetes (T1D) can be largely attributed to vascular inflammation and cardiovascular disease (CVD) that are promoted by the installment of a chronic inflammatory state of the endothelium (Devaraj S *et al*., 2007). Furthermore, diabetic patients experiencing frequent episodes of diabetic ketoacidosis have an increased incidence of morbidity and mortality due to vascular complications and cerebral edema (White NH, 2002; Bialo SR *et al*., 2015). In T1D, concentrations of ketone bodies can reach 25 mmol/L (Laffel L, 1999), as compared to low millimolar concentrations (< 7 mmol/L) induced by prolonged starving on obese volunteers (Owen OE *et al*.,1969) or during post exercise ketosis (Koeslag JH *et al*., 1980).

III.7.3.2 Ketogenic diet and low BHB levels positively affect cardiovascular function

Obesity is a predisposing factor to cardiovascular pathologies including coronary heart disease and hypertension (Seravalle G and Grassi G, 2017; Zheng Y *et al*., 2017). As a KD could decrease body weight, indirect beneficial effects on the cardiovascular function may ensue. KD has an impact on the synthesis of endogenous cholesterol. 3-hydroxy3-methylglutaryl–CoA reductase 2, an enzyme transcriptionally promoted by insulin, leads to the synthesis of β-hydroxy-β methylglutaryl-CoA, which is a precursor for hepatic ketone body production as well as endogenous cholesterol synthesis (Paoli A *et al*., 2013).

KD has also been shown to exert some effect on changes in blood pressure. A 48-wk study reported an improvement in systolic and diastolic blood pressure in overweight participants on a KD compared to a control group on a low-fat diet with the addition of orlistat (Mayer SB *et la*., 2014). Decreased systolic blood pressure was observed after 3-mo of a KD, and the decrease persisted even after a year (Cicero AF *et al*., 2015).

III.7.3.3 The influence of ketone bodies on the myocardium

Cardiomyocytes are structural units of the heart that similarly to oxidative skeletal muscle have a high density of mitochondria. With such an abundance of mitochondria, the myocardium is capable of oxidizing various substrates to produce ATP. Acetyl- CoA from glucose (*via* glycolysis) or lipids (*via* β-oxidation) enters the Krebs cycle. Ketone bodies, generated by the liver, also constitute major acetyl-CoA precursors for the heart (Abdul Kadir A *et al*., 2020).

As ketone bodies are not able to complement the intermediates of the Krebs cycle, these intermediates are constantly lost. Thus, ketone body oxidation is cataplerotic as it leads to depletion of the Krebs cycle intermediates and impairment of the metabolic efficiency (Koeslag JH *et al*., 1980). This cataplerotic effect must be balanced by anaplerotic substances such as circulating glucose, glycogen, or glucogenic amino providing pyruvate (Abdul Kadir A *et al*., 2020) with heart pyruvate carboxylase being the key anaplerotic enzyme in the heart (Des Rosiers C *et al*., 2011).

III.7.4 Ketogenic diet ameliorates axonal defects and promotes myelination in Pelizaeus–Merzbacher disease

III.7.4.1 Ketogenic diet improves pathology in a PMD model with preserved BBB integrity

The consumption of a high-fat/low-carbohydrate ketogenic diet causes the liver to generate ketone bodies. In the brain, ketone bodies such as beta-hydroxybutyrate facilitate sterol synthesis (Koper JW *et al*., 1981) which is essential for myelin membrane growth (Saher G *et al*., 2005). Thus, we asked whether a ketogenic diet that promotes CNS lipid metabolism under conditions of preserved BBB function (Freeman J *et al*., 2006b; Koper JW *et al*., 1981; Puchalska P and Crawford PA, 2017) is also effective in hypomyelinating disease. Plp1tgB and control mice were given a ketogenic diet (KD) or standard a chow diet (SD) between 2 and 12 weeks of age and physiological parameters were monitored weekly. Already after 7 days of dietary intervention with KD, blood levels of ketone bodies strongly increased (about fivefold) and serum glucose dropped to about 70% of the level in SD fed mice. Ketone bodies are imported into the brain by monocarboxylate transporters, mainly MCT1 expressed by endothelial cells (Leino RL *et al*., 2001).

III.7.4.2 Ketogenic diet ameliorates mitochondrial abnormalities in axons of PMD mice

It is unlikely that the moderately improved myelination explains the dramatic improvement in motor functions in KD fed Plp1tgB animals. In PMD patients, motor development is strongly retarded, and progressive axonal loss likely causes the gradual decline of motor functions already achieved (Sarret C *et al*., 2018). In accordance, the frequent axonal swellings (spheroids) in Plp1tgB mice were strongly reduced when feeding a KD. In addition,

we observed in Plp1tgB mice that many axons contained enlarged mitochondrial profiles, as observed before in other models of PMD (Hogan V *et al*., 2009; Nguyen HB *et al*., 2018; Ruiz M *et al*., 2017).

III.7.5 Autism Spectrum Disorder

The prevalence of ASD is significantly higher in people with DS compared to the typical population (Moss *et al*., 2013). Studies report ASD to have an approximate prevalence of 10-18% in individuals with DS (Carter JC *et al*., 2007; Hepburn S *et al*., 2008), compared to 1% in individuals without DS (Christensen DL *et al*., 2016). Individuals with DS and ASD experience poor social orientating, poor integration of verbal and nonverbal behaviors, and limitations in expressive language and adaptive behavior (Rachubinski AL *et al*., 2017). Studies have looked into the KD as a potential therapeutic option in children with ASD. Evangeliou et al. conducted a pilot prospective follow-up study analyzing the role of the KD in 30 children with ASD aged 4-10 years for 6 months. They reported improvements in the Childhood Autism Rating Scale in 18 of the 18 children who adhered to the diet for the duration of the six-month study (Evangeliou *et al*., 2003). This study provided preliminary evidence for the efficacy of the KD as a potential additional or alternative therapy for ASD. Recently, El-Rashidy *et al*. compared the effect of the KD versus a normal diet in a group of 45 autistic children who were 3-8 years of age. The KD group showed significant improvement in Childhood Autism Rating Scale scores. The total Autism Treatment Evaluation Test questionnaire (ATEC) scores were significantly decreased from 41.70 ±5.52 to 33.70 ± 4.2 following implementation of the KD, indicating a decrease in severity of ASD symptoms seen in these children (El-Rashidy *et al*., 2017).

III.7.6 Cognition and Behavior

The KD diet has been effective in treating glucose transporter protein 1 deficiency syndrome and pyruvate dehydrogenase complex deficiency. Studies have investigated effects on cognition and behavior after KD implementation in these individuals. Ramm-Peterson *et al*. implemented the KD for 6-17 months in 6 patients diagnosed with glucose transporter protein 1 deficiency syndrome. Patients in the study had early-onset seizures and developmental delay. All 6 patients demonstrated improvements in general alertness, expressive language, articulation, and physical endurance shortly after starting the KD (Ramm-Pettersen *et al*., 2014). All patients responded to the KD with >90% seizure reduction. Movement disorders also improved shortly after dietary intervention. Interestingly, younger patients showed the greatest improvement in cognition particularly with respect to receptive language, expressive verbal

language, and cognitive index, yet adults did achieve improvements as well (Ramm-Pettersen *et al*., 2014).

The KD is potentially beneficial in the areas of neurobehavioral development, emotional, and social behaviors, and life ability in children with global developmental delay (Zhu *et al*., 2017). Zhu *et al*. conducted a prospective case-control study for hospitalized children with global developmental delay who were divided into a KD treatment group or a conventional treatment group. Both groups received comprehensive rehabilitation training and were assessed with the Gesell Developmental Scale, Chinese version of the Urban Infant-Toddler Social and Emotional Assessment/Achenbach Child Behavior Checklist, and Infants-Junior High School Students' Social Life Abilities Scale before and after 3, 6, and 9 months of treatment. The KD treatment group had significantly greater improvements in the scores of the adaptive, fine motor, and language quotients of the Gesell Developmental Scale compared with the conventional treatment group at all 3 time points. The KD treatment group also had significantly greater improvements in the Chinese version of Urban Infant- Toddler Social and Emotional Assessment/Achenbach Child Behavior Checklist scores than the conventional treatment group. After 9 months of treatment the KD treatment group had greater improvements on the Social Life Abilities Scale. The authors concluded that the KD can improve neurobehavioral development and emotional behaviors in children with global developmental delay, with few adverse effects (Zhu *et al*., 2017).

Conclusion

Conclusion

The ketogenic diet is a useful therapy for patients with intractable epilepsy, including some of the catastrophic epilepsies in infancy and childhood. Its efficacy is at the very least, comparable to anticonvulsant medications (Freeman *et al*., 2006b). It can be used with all ages without harm and with diseases other than epilepsy, the physicians should benefit from the many experiences learned from its use with epilepsy. The change and development in the components and ratios of the KD components, as well as the multiplicity of its types, opened the way for specialists to use it with many illnesses and give very encouraging results.

The KD is one of the available options for those who want to reduce weight and those who suffer from type 2 diabetes. Reducing CHO intake with an LCD is effective in reducing body weight and, in patients with type 2 diabetes, improving glycemic control, with a stronger effect with a very low carb diet (KD). However, excessive use of LCD can be dangerous to the health of people with type 2 diabetes. It is necessary to balance the potential increase in cardiovascular risk because of the unfavorable lipid profile observed with LCD with the benefits deriving from weight loss and improvement of glycemic control. Likewise, the results of using keto and LCD for a long time are still under study and research.

There are multiple mechanisms through which ketone bodies might impact severe viral infections such as COVID 19 disease. A recent review article exhaustively summarizes this concept, proposing the administration of exogenous ketones to critical patients in order to target respiratory virus's complications as a possible therapy (Stubbs *et al*., 2020). The KD-induced increase in endogenous ketone bodies could represent a more valuable strategy for preventing Sars-Cov2 infection and adverse outcomes in obese patients. Especially with the absence of an appropriate pharmaceutical treatment, an alternative can be found in diets such as KD.

While obtaining tangible results for the effect of KD and ketone bodies in neurodegenerative diseases, but most of these results are the result of studies in the laboratory or on animals, and only a few through studies conducted on volunteers. Therefore, it is difficult to consider these results appropriate for humans. Further studies are necessary, especially for research of long-term KD effects on the symptoms and course of neurodegenerative diseases.

The perspective of the use of KD in various diseases has been growing recently. Abnormal glucose metabolism uptake, diminished mitochondrial-associated brain energy metabolism, changes in neurotransmitter release, and increased inflammatory response are the key pathophysiological metabolic alterations observed in AD. The KD can modify many pathological factors of neurological diseases to normal or close. Based on the limited animal studies and clinical trials, KD has beneficial effects for enhancing mitochondrial function and

cellular metabolism. It is associated with improved cognitive performance in elderly adults with AD.

The anti-tumor mechanisms through which the KD, CR (and intermittent fasting), and other potential metabolic therapies act are not completely understood; however, the animal model data strongly suggest that metabolic alteration may be a highly effective therapy as well as a potent adjuvant to the current standard of care for malignant brain tumors. The KD and/or CR are the only therapeutic approaches that simultaneously target multiple hallmarks of cancer such as energy metabolism, angiogenesis, and inflammation.

As we have seen in this study, there are many other uses of KD in many diseases, as it gave good results, knowing that there are many studies that have been done in the laboratory and it is difficult to apply them to humans. With this, there is great optimism with the increasing interest of specialists in the medical use of KD and knowledge of how it works, with many studies and experiments.

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