KETOGENIC DIET AND GENETIC DISORDERS

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Abstract

Ketogenic Diet (KD) represents a specific type of diet which is based on the process of ketosis. Even since 1925, KD began to be used as a treatment for drug-resistant epilepsy but recently, KD has begun to take part in the treatment of many chronic diseases. In this review we look at the role and the implications of KD in some genetic disorders: pharmacoresistant epilepsy, Alzheimer's disease, Angelman syndrome, glucose transporter type 1 deficiency syndrome (Glut1-DS), glycogen storage diseases (GSDs) and pyruvate dehydrogenase complex deficiency (PDCD). The review aims to provide clinicians a snapshot of the genetic factors that could have an impact on the response to patient's response to KD. As genetic variants may influence the response to KD, the implementation of nutrigenomics in the personalized nutrition of the patient with KD would be the key for the best patient care.

Keywords: ketogenic diet, genetic disorders, epilepsy, gene

Introduction

Ketogenic Diet Therapies represent a group of high-fat, low-carbohydrate diets which are based on the process of ketosis. Currently, there are four types of ketogenic diet therapies: the classical ketogenic diet (KD), modified Atkins diet (MAD), medium chain triglyceride (MCT) and, also, low glycaemia index treatment (LGIT). [1]

During ketosis, in the human organism is produced a form of starvation, a state that deviate from the traditional source of energy-the glucose to fats. By limiting the carbohydrate intake to a total amount per day of 10 to 50 grams (5% to 10% of total caloric intake), the human body is forced to use fats as a source of energy for cells, tissues, and organs. [1]

Even since 1925, KD began to be used as a treatment for drug-resistant epilepsy. Recently, KD has begun to take part in the treatment of many chronic diseases such as diabetes, cancer, obesity, polycystic ovary syndrome, neuromuscular and neurological diseases, and many studies demonstrating the positive effects of KD. [2]

Genetic factors may influence the body's response to KD, by affecting the metabolism of carbohydrates and fats. Common genetic variation consisting in single-nucleotide polymorphism (SNPs) may interact with individual differences and impact the response to KD.

Aim

The aim of this review is to discuss the implications of KDs in a few selected genetic disorders. Although there are several genetic disorders in which KD has a huge impact as a therapy, the diseases chosen to be discussed in this review are epilepsy, Alzheimer disease (AD), Angelman syndrome (AS), glucose transporter type 1 deficiency syndrome deficiency (GLUT1-DS), glycogen storage diseases (GSDs) and pyruvate dehydrogenase complex deficiency (PDCD). By making a brief synthesis of the current implications of KD in the treatment of these disorders, we would like to gain a better understanding of the importance of KD and the way it interacts with genetic factors. Also, the review aims to provide clinicians a snapshot of the genetic variants that could have an impact on the response to KD in the genetic disorders that were taken into consideration.

Material and method

The browse platform used was PubMed and the search terms were "ketogenic diet", "genetic disorders", "genes" (August 2021) The articles used as references were filtered by data publication as there were only taken into consideration those published in the last 5 years.

Results

Cell physiology

The energy of the cell is produced in the organelle called mitochondria. The mitochondrial metabolism involves the oxidation of pyruvate, the citric acid cycle, β-oxidation of fatty acids and the oxidative phosphorylation. In the presence of oxygen, the energy source of the cell is glucose. Through glycolysis, glucose is transformed into pyruvate and then, inside mitochondria, takes places the oxidation process through oxidative phosphorylation which lead to ATP production. In the absence of glucose, the cell is taking energy from the degradation of fatty acids and proteins, which results in generation of the ketone bodies. The three most important ketone bodies are acetone, acetoacetate and 3-β-hydroxybutyrate. Ketone bodies are produced when there is not sufficient glucose in the organism, for instance during fasting process, prolonged exercise, or when following a ketogenic diet. In the mitochondria of the liver cells takes place the ketogenesis process with the generation of ketone bodies, which are transported via blood to different organs of the body. [3]

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In normal conditions, the concentration of the ketone bodies in the blood is very low (<0.3 mmol/L). Following a ketogenic diet, when ketone bodies' concentration in the blood reach around 2-4 mmol/L, the tissues begin to use the ketone bodies as a source of energy. What is interesting is that ketone bodies produce an even higher quantity of energy compared to glucose and this is due to the modifications in the ATP's production they can induce. Moreover, it has been demonstrated that ketone bodies have pleiotropic actions, being implicated in pathways and gene expression of different processes in the body such as oxidative stress, inflammation, immune function, cell signaling, membrane health and antioxidant status. [4, 5]

Precision Nutrition and Ketogenic Diet

As personalized nutrition is becoming more and more popular nowadays, the personalized approach of KD would maximize the effectiveness as a therapy and would ensure long-term safety for the patients. Although several clinical trials proved the efficacy of KD, the therapeutic response to KD has proven to be different for each individual. Besides the variability regarding sex and age, there is the interaction between genetic factors and lifestyle which include diet, activity level, and insulin resistance. Genetic factors may influence the body's response to KD, by affecting the metabolism of carbohydrates and fats. Common genetic variation consisting in single-nucleotide polymorphism (SNPs) have an effect that depend on the interaction with environmental factors and other genetic variants. In the past years, there are a few GWAS (genome-wide association studies) that managed to identify SNPs associated with individual response to KD. [5]

Epilepsy

It is estimated that there are around 50-60 million people that suffer from epilepsy, 25-30% of these being resistant to any pharmacological treatment. Over the last years, concerns about side effects of the medications, the negative effects that seizures have on the brain development and also, concerns about treatment failure, has led to a revolutionary growth in the use of KD as a therapeutically alternative for non-responsive epilepsy in children, adolescents and adults. Studies demonstrated that after 3 months, half of those on KD had more than 50% reduction in seizures. Moreover, patients reported improvements in the quality of life and, also, possibility to reduce or interrupt medications. [3]

Certain types of epilepsy such as tuberous sclerosis, myoclonic-atonic seizures, Dravet syndrome are known to have a good response to KD. [6]

A review published in February 2021 mentioned that 6 randomized control-trials proved the efficacy and safety of different KDs in patients with intractable epilepsy. The positive effect of KD that was reported by all the 6 studies, was the reduction in seizures frequency. The side effects reported were constipation, diarrhea, vomiting, hypercalciuria, hyperlipidemia and weight loss. [1]

As we live in the era of genomics, evidence is showing that identifying specific mutations in the genome is relevant both for diagnosis and prognosis as well as it is for treatment selection. This is applicable in epilepsy as well. For instance, in Dravet Syndrome due to mutations in SCN1A, KD proved to be efficient as an adjuvant therapy. On the other hand, in patients with epilepsy caused by autosomal dominant variants in KCNT1 (a gene that encodes the potassium channel) response to KD is quite poor. Moreover, two retrospective studies showed that patients with CDKL5-related epilepsy, either were completely unresponsive to KD, or their response was quite favorable, reducing the seizures frequency. [7, 8]

A GWAS published in 2018 aimed to determine whether common genetic variation influences the response to KD in children with epilepsy and discovered that a SNP within CDY1L (chromodomain Y 1 ligand) may affect KD response to seizure. The patients with epilepsy received KD and after a 3 month follow up, the GWAS which included 123 responders to KD vs 112 no responders identified an association locus of CDYL (rs12204701) at 6p25.1. Patients carrying at least one copy of CDYL1 A allele had a lower response to KD compared with non-carriers. CDY1L is a protein and acetyltransferase which is very important in the brain, in the epigenetic regulation of genes expression. [9]

Alzheimer's disease (AD)

Alzheimer's disease is one of the top ten causes of death in USA and, unfortunately, is still the only one without a specific treatment. At least 99% of drug candidates fail. [10]

Although AD cannot be considered a rare disease, it has been established that genetic factors may contribute to its etiology. The greatest genetic risk factors for AD is represented by the mutations of apolipoprotein E (ApoE). Apo E is a protein synthesized primarily by astrocytes but also by other glial cells and has a very important role in the metabolism and transport of lipids in the body. It is estimated that around 20% of the normal population carry ApoE4 allele and around 40-65% of AD cases, ApoE4 allele representing the genetic factor that led to late-onset AD. [11]

Ketogenic diet, by increasing 3-β-hydroxybutyrate so that it can be an alternative source of energy to glucose, has shown to be efficient in treating the patients with AD. For instance, a recent randomized crossover trial conducted on 26 patients from which 21 followed KD, wanted to determine whether the KD followed for 12 weeks would improve daily function, cognition, or quality of life of patients with AD. The study concluded that KD proved high rates of retention, safety, and adherence and that the quality of life and daily function of patients with AD greatly improved. [12]

The biological mechanism through which KD can help reduce the risk for AD implies the fact that β-hydroxybutyrate can reduce oxidative stress, inflammation, and mitochondrial dysfunction. Moreover, Qi et al described three mechanisms that can explain the benefits of KD to patients with AD. Firstly, KD increases lipophagy in neurons, protecting against lypotoxicity. Secondly, KD improves lipid transport, decreasing the lipoprotein glycation. Moreover, β-hydroxybutyrate represents an alternative source of acetyl-CoA, which is needed for sustaining brain's metabolic needs. [13, 14]

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A review published in December 2020 remarked that ApoE4 variant could influence the response to KD regarding the cognitive performance. A placebo-controlled trial conducted on 20 patients with AD or mild cognitive impairment showed that administration of medium chain triglyceride (MCT) improved cognitive performance only in ApoE3 homozygous but not in ApoE4 carriers. Also, ApoE4 carriers had more prolonged elevations in ketone levels after MCT administration which suggest that ApoE4 carriers may have a lower cellular utilization of ketogenic agents. This information was further investigated by a larger randomized, placebo-controlled, double-blind study that tested the administration of MCT supplement for a period of 3 months on 152 patients with AD. Interestingly, both carriers and non-carriers ApoE4 showed improvements in cognitive performance, but the effects were better and significantly correlated with β-hydroxybutyrate blood levels only in ApoE4 non-carriers. [¬5]

Angelman Syndrome (AS)

Angelman Syndrome is a genetic neurodevelopmental disorder, which is caused by the deficiency of maternally inherited UBE3A (ubiquitin E3 ligase). Angelman Syndrome is characterized by motor dysfunction, severe developmental delay, language and cognition deficits, frequent smiling and laughter, seizures, as well as autism-like behavior. In most tissues UBE3A gene is expressed from both alleles, whereas in neurons is expressed only the maternally inherited UBE3A allele (the paternally copy being silent). It is known that the maternal deficit in UBE3A gene can have four genetic etiologies: deletions of the maternal 15q11–q13 region (approximatively 70% of cases), paternal uniparental disomic of chromosome 15 (5%), imprinting defects or mutations in UBE3A (10%). [15]

The main physiological pathways that explain the use of KD in patients with Angelman Syndrome involve deregulated GABAergic and dopaminergic neurons, abnormal mTOR signaling, excitation/inhibition imbalance, impairment in synaptic plasticity. Moreover, it has been tested on mice with Angelman Syndrome that KD can improve the hippocampal deficits by stimulating mitochondrial biogenesis. [16, 17]

KD and low-glycemic-index diets proved to have benefic effects in the treatment of drug-resistant seizures in patients with Angelman syndrome, improving the quality of life, cognition, sleep, mobility and, also, the gastrointestinal health. As KD is based on ketosis, it was wanted to know whether the administration of exogenous ketones would have a similar effect as KD. In 2016, a study showed that supplementation with exogenous ketones in mice improved memory, learning, motor coordination and synapse plasticity in mice with AS and was also. Therefore, the study suggested that supplementation with exogenous ketones can produce sustained ketosis and can ameliorate AS phenotype. [18]. Recently, a randomized, placebo-controlled, double-blind, crossover study is being conducted on pediatric population with AS (ages 4-11 years) to study the potential benefits of nutritional intervention with exogenous ketones (β-hydroxybutyrate). The study offers a unique design, providing data for the nutritional approach of patients with AS, helping them to overcome the disease. [19]

Glucose transporter type 1 deficiency syndrome (Glut1-DS)

Glucose transporter type 1 (Glut1) is a protein located in the blood–brain barrier and its main role is to assure the facilitative transport of glucose into the brain, an energy-independent process. Glut1 protein is encoded by SLC2A1 gene, which is located on chromosome 1p34.2. [20]

The glucose transporter type 1 deficiency syndrome (Glut1-DS) was described for the first time in 1991. As the understanding of the pathophysiology mechanism of this disease has significantly improved, the clinical features of Glut1-DS involve transient movement disorders, paroxysmal exertion-induced dyskinesia (PED), myoclonic astatic epilepsy (MAE), absence epilepsies particularly with an early onset absence epilepsy (EOAE), childhood absence epilepsy (CAE), episodic choreoathetosis and spasticity (CSE) and, also, focal epilepsy. [20]

KD, as precision medicine therapy should be started in the early stages of the Glut1-DS. A general review about Glut1-DS explained the mechanisms through KD can have beneficial effects. These mechanisms include stabilization of synaptic function, reduction in the generation of reactive oxygen species, boosting energy production, seizure reduction. Regarding the cognitive functions and neurodevelopment, there is not enough evidence for positive effects of KD. [21]

The classical KD assume that the serum ketones should be maintained around 3–4 mg/dl, but at this level, side effects such as fatigue or diarrhea might be intolerable. Therefore, in cases of noncompliance to KD or when the patients are reluctant, a modified KD like Atkins diet might be better option. The modified Atkins diet imply that 65% of total calorie intake is provided by high food fats, restricts carbohydrates at 10g/day (15g for adults), but does not restrict protein or calorie intake. Although there is enough data that suggests the benefits of the modified Atkins diet, its effect has not been tested on huge number of patients with GLUT1-DS [20, 21].

A recent observational descriptive study, published in March 2021, was conducted on 18 patients with GLUT1-DS (with or without mutation in SLC2A1) to investigate the beneficial effects of KD. The conclusions of the study were that KD, as well as the Modified Atkins Diet were effective for the patients enrolled in the study, from which six were SLC2A1 positive. Also, the most frequent side effects were constipation, hyperlipidemia and hypercalciuria. [22]

Regarding the genetic testing in GLUT1-DS, the SLC2A1 gene mutations are detected only in 70-80% of patients with the disease. For instance, in a Japanese study published in 2011, 33% of patients with clinical symptoms of GLUT1-DS, were not found to have mutations in exons of SLC2A1 gene. [23] Furthermore, in 2016 a study suggested that low cerebrospinal fluid glucose levels might be associated with pathogenic variants in SLC2A1, which also include the deep intronic variants. By this, the study encouraged the extension to non-coding regions, enabling the

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diagnosis of GLUT1-DS so that the patients can benefit from KD therapy. [24]

The idea that the absence of pathogenic mutation in SLC2A1 gene (common variation) does not exclude GLUT1-DS, was sustained by some case reports. For instance, in 2017 it was reported a novel heterozygous variant in the exon 5 of SLC2A1 gene, detected by Sanger sequencing.[25] Also, in children, there were found de novo and heritable paternal mutations of SLC2A1 gene, including amino acid insertion and point mutations. [26]

Recently, by whole genome-sequencing, rare homozygous missense variants were detected in SLC45A1 (second cerebral glucose transporter) which can cause epilepsy and intellectual disability. Regarding the treatment, KD might be effective in SLC45A1 mutations as well, but it needs further investigations. [26, 27]

Glycogen Storage Diseases (GSDs)

The hepatic glycogen storage diseases represent a group of diseases characterized by an inborn error of metabolism, more exactly abnormalities of the enzymes implicated in the degradation or the synthesis of the glycogen. [28]

The first GSD was described in 1929 by Edgar von Gierke. Until now, we know that there are about 16 GSDs (type 0 to type XV). All the types of GSDs are characterized by hypoglycemia due to an abnormal conversion of glycogen into glucose. [28]

Although the treatment recommendations in GSDs are based on the specific enzyme defect in each type, nutritional therapy remains the primary treatment for GSDs. The goal of managing all the hepatic GSDs is to prevent hypoglycemia as well as to minimize acidosis. High-carbohydrate diets could prevent fasting hypoglycemia, but the main issue is that increases glycogen storage and, also, the progression of muscular and cardiac manifestations. [28, 1]

Recently, there are several publications that emphasized the positive outcomes of KD in the management of GSDs. For instance, several case reports documented beneficial effects of KD in GSD III even since 2014. GSD III represents an autosomal recessive disease and is caused by the deficiency in glycogen debranching enzyme which is encoded by AGL gene. Clinically, GSD is characterized by affected liver, skeletal muscle, and heart. In 2019 a case report showed that Modified Atkins Diet was very efficient in treating a patient with GSD IIIa, improving quality of life, physical activity, cardiomyopathy, unlike other hyper carbohydrate diets. [29] Also, in 2020, a 4-year follow-up case report, concluded that KD is safe and could reverse the cardiomyopathy and improve quality of life in patients with GSD III. [30, 1]

GSD V, also called McArdle disease is caused by genetic defects of glycogen phosphorylase, a muscle specific isozyme, which lead to incapacity of glycogen to be converted in ATP in skeletal muscles. Patients with GSD V present exercise intolerance. In 2020, a pilot study that a modified KD (consisted of 75% fats and 10% carbohydrates) induces ketosis, leading to improvements in exercise tolerance and fatty acid oxidation. [31]

GSD VII, or the Tarui disease, is caused by a deficiency in muscle phosphofructokinase (PFKM) and is characterized by myalgia and exercise intolerance. The first study that showed a long-term effect of KD in this disease, was represented by a case report with 5 years follow up on modified Atkins diet. Published in 2020, the study concluded that KD alleviated the muscle symptoms, had beneficial effects on breathing and improved exercise performance and oxygen uptake. [32]

Pyruvate Dehydrogenase Complex Deficiency (PDCD)

The pyruvate dehydrogenase complex deficiency (PDCD) represents a rare neurodegenerative disorder which is caused by genetic alterations in any of the genes encoding the enzymes involved in the complex. The enzymes involved in the pyruvate dehydrogenase complex (PDHc) have the role of catalysts in the decarboxylation of pyruvate into acetyl-CoA. The pyruvate dehydrogenase complex deficiency (PDCD) is, actually, a metabolic disorder and clinically, is characterized by progressive neuromuscular and neurological degeneration and also, lactic acidosis. [1]

Ever since 1976, KD was proved to be beneficial in pyruvate dehydrogenase complex deficiency (PDCD). Since then, the efficacy of KD has been shown by several case reports. [1]

Recently, an article released in October 2020 concluded that identifying the causing mutations for PDCD and understanding the structural and functional mutant variants, would allow to have an insight of the clinical phenotype and also to select the best option for treatment. The study was conducted on thirteen Portuguese patients and the mutations found among them were in PDHA1, PDHX and DLD genes. All the patients received treatment which included ketogenic diet, antiepileptic drugs and also thiamine supplementation. Three patients with PDHX mutations and three patients with PDHA1 mutations clearly showed beneficial effects following KD. [33]

Conclusions

KD has an important role in the treatment of epilepsy, Alzheimer's disease, Angelman syndrome, GLUT1-DS, GDSs and PDCD. As there is evidence regarding the benefits of KD, medical practitioners should take into consideration KD as adjuvant therapy for these disorders. Also, as the response to KD is highly correlated with genetic variants, implementation of nutrigenomics in precision medicine would be the key for the best management of the patient.

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