



KETOGENIC DIET – FROM THE IMPLEMENTATION IN CLINICAL PRACTICE TO NOWADAYS

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ABSTRACT

Introduction: The ketogenic diet (KGD) is a high-fat, adequate-protein, low-carbohydrate diet. In 1920's the diet was developed to treat difficult-to-control epilepsy in children. Nowadays its efficacy has been proven in many other diseases, such as metabolic disorders, brain tumours, autism, Rett syndrome, and in other areas, it has been actively studied.

Aim: The aim of this article is to represent the historical review of the therapeutic implication of KGD, as well as to reveal the contemporary clinical trends in which it is being used.

Material and Methods: A literature review of 96 scientific reports in English has been made.

Results and Discussion: The KGD was developed in the early 1920s. In the period 1970-1990, the therapeutic use of the diet was discontinued, due to the breakthrough of the new anticonvulsants for epilepsy. The interest in KGD was recovered after a meeting of the "American Epilepsy Society" in 1996.

The diet demonstrates anticonvulsant efficacy in epilepsy therapy. According to a survey in 2013, the incidence of seizures among half of the number of children was reduced by at least a half, and 15% of them were completely discontinued. The diet is also used in the treatment of metabolic diseases, such as GLUT 1-deficiency syndrome, reducing the incidence of seizures, improving muscle coordination and concentration. It is also effective in pyruvate dehydrogenase deficiency syndrome by replacing the major energy source - glucose with ketones. Along with these, it is also used in patients with autism (in approximately 60% of patients it improves learning ability and social skills), Rett syndrome, Alzheimer's disease, Parkinson's disease, and others. Its mechanism of action is not fully clarified, as well as its degree of effectiveness in some areas.

Conclusion: The ketogenic diet is widely implemented worldwide. It comprises a tremendous therapeutic potential that has been growing considerably during the past decades.

Keywords: ketogenic diet, historical data, therapeutic potential

Introduction

The ketogenic diet (KGD) is a high-fat, adequate-protein, low-carbohydrate diet. It was developed in the 1920s to treat difficult-to-control epilepsy in children. Nowadays, its efficacy has been proven in a variety of diseases, such as metabolic disorders, brain tumours, autism, Rett syndrome, and in other areas, it has been actively studied. Its effect is to replace the essential energy source for the body - glucose from carbohydrate feed, with ketones produced by the catabolized fatty acids. An elevated level of ketone bodies in the blood is a state known as ketosis in which basic ketones are acetoacetate and β -hydroxybutyrate. The diet demonstrates an anticonvulsant effect, influences hyperinductivity of brain activity, increases the ability of concentration, etc. The mechanisms of therapeutic effects are not fully understood. One of the scientific hypothesis is that the ketones produced to contribute to the production of γ -aminobutyric acid GABA, which is a major inhibitor of neurotransmitters in human brain. It helps to balance brain activity, improves concentration ability and reduces chronic anxiety. Until now, this hypothesis has not been fully demonstrated, there are scientific reports that have controversial results and many researchers work on different strands associated with low glucose levels, increased intake of polyunsaturated fatty acids, etc. [1, 2]. These mechanisms are demonstrated in other authors' works.

Historical data – from implementation in medical practice to nowadays

KGD was developed at the beginning of 1920. The first scientific papers [3, 4] date from 1921-1923, according to which the use of ketogenic diet leads to a change of brain metabolism, which helps in reduction of seizures in both children and adults.

In 1970-1990 the therapeutic use of the diet was discontinued as a result of the rapid development of new anticonvulsants for epilepsy [5, 6]. The interest in it returns

after a meeting of the American Epilepsy Society in 1996 [5].

The therapeutic application of the diet has resumed over the past 15-20 years, thanks to Charlie's foundation and their film "First do no harm" (1997). The film is starring American actress Meryl Streep and recreates the real story of a boy suffering from drug-resistant epilepsy and successfully treated with a KGD. There is a growing interest in the diet after the premiere of the film.

In 2006, during the annual meeting of "International Child Neurology Association" a separate section of reports on KGD was created for the first time. Two major conferences dedicated to this type of treatment Phoenix, Arizona and Edinburgh, Scotland, were organized in 2008 and 2010 with a few hundred attendees. Nowadays, the therapeutic application of KGD is present in more than 50 countries worldwide [7, 8], and according to Freeman JA et al. (2007), it is likely to be more effective than most newer drugs in this area at present [5].

Clinical implementation of ketogenic nutrition

KGDs have a long history in refractory epilepsy treatment, but to date, its use has expanded considerably and is actively investigating its effects on increasingly new clinical trends.

• Epilepsy

In recent years there has been a renewed interest in the application of KGD from pediatricians, neurologists and epileptologists to treat the disease, especially in children and adolescents. A number of studies have been conducted to elucidate the role of food in algorithms for treatment of various epileptic syndromes [9].

The ketones formed during carbohydrate starvation (in the absence of enough glucose) lead to the oxidation of some acids that act anticonvulsively. Authors of the university hospital "Johns Hopkins Medical Institutions" (Baltimore, USA) report results from 150 children with epilepsy treated with KGD [10, 11]. Twelve months after the start of the diet, 7% of the children were seizure-free, 20% had 90% decline in seizure frequency. 55% discontinued dietary compliance during the first six months because they consider it difficult to apply or not effective enough. Three to six years later, 27% of children who continue to adhere to the KGD have had little or no seizures. Most children currently do not apply the diet, and even some of them have stopped taking medications [5].

Another study conducted by Kossoff E and Wang H (2013), shows that approximately half of children the seizure frequency is reduced by at least half and approximately 15% of seizures are halting [12].

• Autism

Symptoms of Autism Spectrum Disorders refers to a range of conditions characterized by impaired ability to communicate, stereotypical movements and communication deficits. Incidence rates are increasing, and current treatments are often ineffective. KGD can be used as additional or alternative therapy among children with autistic behavior [13]. According to Napoli (2014) and other authors [14, 15] one of the reasons for the therapeutic effect

is the increased GABA output [18]. A number of authors claim that the effect of dieting is reported to vary degrees in approximately 60% of children [13] – they are being tested with the "Childhood Autism Rating Scale". There is an improvement in learning and social skills [13, 16, 17].

• GLUT 1 – Deficiency Syndrome

The syndrome is a rare genetic disease, which is expressed in protein GLUT 1 deficiency, promoting blood glucose to the brain. Symptoms begin shortly after birth and include a delay in development, difficulty in movement and sometimes seizures. Unlike glucose, ketones do not need protein to pass from blood to brain. KGD reduces the incidence of seizures, improves muscles coordination and concentration [16, 18, 19, 20, 21].

• Pyruvate dehydrogenase deficiency

The syndrome is characterized by the inability of PDHD to be metabolized to Acetyl – CoA, resulting in a heterogeneous clinical picture characterized by hypotension, lethargy, apnea, etc. [22]. Patients are provided with ketones that bypass the metabolic defect and serve as an alternative fuel for the brain by applying KGD [23].

• Brain tumors

In 2010 reports in medical literature proved the role of KGD in decline of brain tumours. The study conducted by Stafford et al. [24] and Zuccoli et al. [25] report for survival of an adult patient with glioblastoma multiforme after a two-month restraint period by using KGD and vitamin and mineral supplements. There was an evidence of tumour recurrence 10 weeks after the onset of strict dietary therapy. The concept of implementation of KGD is based on the idea that the change of the basic energy substrate glucose with ketones disturbs tumour metabolism while maintaining the nutrition status of patients [8]. Other scientists keep the belief that since tumour cells are more dependent on glycolysis than normal cells, causing a condition of ketosis in the patient, this would lead to the death of tumour cells [26, 27].

• Parkinson's disease

KGD is believed to bypass the involvement of mitochondrial complex I (included in pathogenesis in some forms of the disease). The beneficial effects of the diet, demonstrated in a number of clinical cases, need to be further investigated in controlled studies. It is important to foresee how potential dietary changes affect levopoda absorption – a drug used to treat the disease [20, 28].

• Schizophrenia

In 1966 Dohan F. [29] reported a low incidence of schizophrenia in countries which restricted bread consumption during World War II, suggesting a possible link between bread/cereals and schizophrenia [30]. Other researchers noted a link between schizophrenia and celiac immune-mediated enteropathy induced by gluten intake containing cereals [1, 31]. Nowadays, there have been several clinical trials that note the therapeutic effect of KGD on the psychotic manifestations of schizophrenia and bipolar disorder.

According to Kraft B. & Westman E. (2009) [30], the possible reasons for the effective influence of KGD on schizophrenic symptoms include metabolic consequences

of gluten elimination from the diet and modulation of schizophrenic disease at the cellular level. According to Murphy P (2004) KGD also has therapeutic effect on depression – a common symptom of schizophrenia and bipolar disorder [32] The direct effect on GABA levels (the mechanism is explained above), is well-studied in patients with depression and to date are thought to be genetically related to schizophrenia and bipolar disorder [33]. Yoon et al. reported a significant reduction in GABA levels in patients with schizophrenia [34].

• **Other**

Other areas where KGD has a potential therapeutic effect include Lafora disease, Landau-Kleffner syndrome, Sturge-Weber syndrome, Rett syndrome, Angelman syndrome, West syndrome, tuberous sclerosis, migraine, etc. There are separate reports describing the use of KGD in some rare metabolic conditions such as glycogenosis type V [35], phosphofructokinase deficiency [17] and mitochondrial respiratory disturbances [8].

Patients with diseases including known or conjectural glucose metabolism disorders, such as type II diabetes and polycystic ovary syndrome, have been reported in a series of cases in favour of KGD.

Henderson et al. [36] reported a significant improvement in cognitive performance in patients with Alzheimer’s disease treated with KGD [12]. A medical food called Axona is currently available in the US for treatment of Alzheimer’s disease. It contains fractionated coconut oil, middle chain triglyceride, which aims to alter the metabolic processes associated with mild to moderate Alzheimer’s disease, providing an alternative source of energy for the brain. The brain ability to use glucose as a regular source of energy during the disease is impaired but using Axona the coconut oil decomposes to ketones, which provide an alternative source of energy.

There are few animal model studies and uncontrolled which suggest the potential benefits of KGD in patients with amyotrophic lateral sclerosis, narcolepsy, etc. [8]. There is a lack of sufficient evidence of KGD efficiency in these areas [37].

Diet regimen and side effects

In order to achieve a therapeutic effect, it is necessary to adhere to the ketogenic regime for a minimum of 6 months [13] to one year [10] with its application after this period the therapeutic effect may keep increasing [11].

KGD is contraindicated in some diseases, especially in patients with impaired fat metabolism, as this may lead to severe metabolic crisis. Therefore, additional studies are required for clinical tests in order to exclude congenital metabolic errors (delay in development, hypotension, exercise intolerance, myoglobinuria, cardiomyopathy) if there is a clinical suspicion for metabolic abnormalities before the onset of KGD [17] (Table 1).

Table 1. Some metabolic disorders in patients that can be aggravated by ketogenic diet therapy

medium-chain acyl dehydrogenase deficiency
medium-chain 3-hydroxyacyl-CoA deficiency
long-chain acyl dehydrogenase deficiency
long-chain 3-hydroxyacyl-CoA deficiency
deficiency of pyruvate carboxylase
carnitine deficiency
porphyria
some mitochondrial defects

According to some authors, the side effects include constipation, dyslipidemia, growth retardation, acidosis [12], etc. In some patients, gastrointestinal symptoms may occur (eg. reflux) [38], including also hypoproteinaemia and increased susceptibility to infections. Woody reports for an increased incidence of infections that occurred in 2-4% of children treated with KGD due to abnormal neutrophil function with impaired bacterial phagocytosis [39].

Some patients may experience an increased risk of renal stone disease (3-7% of children treated with KGD). The kidney stones formation may be associated with hypercalciuria and hypocitraturia due to KGD. The liquid limitation is an additional factor that could influence the process. The oral administration of potassium citrate is an effective prevention against kidney stones formation, reducing the risk up to seven times [40]. There is also evidence of an increased risk of development of cardiovascular diseases due to increased levels of β -hydroxybutyrate and high acidosis which can lead to heart abnormalities (Table 2).

Table 2. Diseases and side effects due to ketogenic diet

constipation
vomiting
diarrhea
abdominalpain
kidneystones
slowgrowth
osteomalacia
cardiomyopathies
hyperuricemia (gout)
hypocalcaemia
hypercalciuria
hypomagnesaemia
acidosis
vitamin D deficiency
hypoproteinaemia
hypoglycemia
hyperlepidemia
carnitinedeficiency
irondeficiencyanemia

lack of energy
increased susceptibility to infections

Some vitamins and minerals that are missing in KGD should be included – vitamins D, B and calcium. Scientists also recommend additional intake of zinc, selenium, magnesium, phosphorus (Table 3).

Table 3. Nutritional supplements recommended by “International Ketogenic Diet Study Group” (Baltimore, Maryland, USA) for patients on ketogenic diet therapy (adapted by [37])

Most often recommended
Multivitamins with minerals (including trace elements)
Calcium with vitamin D
Additionally recommended
oral citrates
Laxatives
additional selenium, magnesium, zinc, phosphorus, vitamin D
Carnitine
oil containing MCT or coconut oil (source of CBT)
salt (for patient over 1 year)
<i>The nutritional supplements listed above should not contain carbohydrates whenever possible. MCT – medium chain triglycerides.</i>

Hartman A and Vining E (2007) argue that potential side effects can be avoided by closely monitoring the patient during the initiation and maintenance of the diet [17]. The side effects of KGD are temporary, manageable and limited, so they rarely require its interruption. However, they are important for the clinician to recognize them successfully and to take timely measures to eliminate them [5].

CONCLUSION

Nowadays, KGD is implemented worldwide. There is an increasing number of annual studies which clarify its biochemical mechanisms, genetic interactions, etc. At this stage, there are no satisfactory outcomes in this direction.

The diet, along with its modifications, has a great therapeutic potential in clinical practice. It should be noted that especially in developing countries, KGD may be an accessible approach to epilepsy therapy compared to anti-convulsant medication [5], the value of which has increased in recent years.

Abbreviation list:

KGD – ketogenic diet

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