A MODERN LOOK AT KETOGENIC DIETS - INDICATIONS AND HEALTH RISKS

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ABSTRACT

INTRODUCTION: The ketogenic diet (KD) is characterized by extremely high fat (F) intake and high carbohydrate (CH) restriction. It is currently used uncontrollably by the population to reduce body weight or body fat.

AIM: This article is an attempt to present the biochemical basis of KD and to summarize data regarding both the indications for its use as well as its undesirable effects and contraindications. Special attention is paid to the safety profile of KD.

MATERIALS AND METHODS: Articles, scientific books and publications related to low-carbohydrate diets and KD were searched in the PubMed database and Google Scholar. Articles published in the last decade were included in the review. The search was conducted with a list of keywords: ketogenic diet, safety, obesity, health, mortality.

RESULTS: Studies of the effect of KD on obesity showed no difference in appetite control and weight loss compared to other isocaloric (but normal carbohydrate) diets. KDs have many contraindications and create health risks. A meta-analysis of cohort studies finds a link between intake of CHs and overall mortality. The lowest risk of death is observed with the consumption of CHs, providing 50-55% of daily energy intake. Mortality is highest with an intake of CHs below 30%. A relatively higher risk of death was found when CHs on the menu were replaced with animal sources of fats and protein, and lower when replaced with vegetable fats.

CONCLUSION: When switching to KD, it is advisable to choose foods containing mostly unsaturated fats as a priority. It is desirable to avoid sources of saturated fatty acids and, in particular, hydrogenated oils rich in trans isomers of fatty acids. A healthier alternative to the classic KD could be the replacement of CHs with vegetable fats and proteins. This eating pattern can contribute to longevity and good health.

Keywords: *ketogenic diet, safety, obesity, mortality*

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INTRODUCTION

The ketogenic diet (KD) is an alternative diet characterized by extremely high fat (F) intake and high carbohydrate (CH) restriction. The first KD models were developed in 1920 by Dr. R. Wilder (Mayo Clinic, USA) to treat type I diabetes and difficult-to-control epilepsy in children. A century ago, diet therapy in these patients was the only treatment because of the lack of effective drugs. Administra-

tion of KD leads to changes in brain metabolism and production of gamma-aminobutyric acid (GABA), which helps to reduce seizure symptoms in epilepsy. Between 1950 and 1990, KDs were left aside because of the availability of new anticonvulsant drugs and insulin. Interest in KD for the treatment of epilepsy in children has been restored following a 1996 meeting of the American Epilepsy Society. In 2008, an international consensus on the application of KD in neurological diseases, including epilepsy in children, was adopted and later, updated in 2018 (1, 2). KDs have significant therapeutic potential and are currently successfully complementing treatment in:

- ◇ diseases of the nervous system (amyotrophic lateral sclerosis, multiple sclerosis, bipolar disorders, some forms of epilepsy and autism, some brain tumours: glioblastoma, astrocytoma, etc.)

Table 1. Energy distribution of different nutrients (in %) in healthy eating and KD, adapted from (3,4,5).

Nutrient	% of total energy intake from following healthy eating	% of total energy intake from following KD
Carbohydrate	45-60	5 (up to 20 in less restrictive KD versions)
Protein	10-20	10
Fat	30-35	70-85

- ◇ some rare genetic diseases (GLUT 1 syndrome, Rett syndrome, etc.)
- ◇ metabolic disorders (polycystic ovary syndrome, etc.)

Therapeutic effect is achieved by adhering to the KD for a minimum of 6-12 months.

AIM

This article aims to present the biochemical base of KD and to summarize data regarding both the indications for its use as well as its undesirable effects and contraindications. Special attention is paid to the safety profile of KD.

MATERIALS AND METHODS

Articles, scientific books and publications related to the low-carbohydrate diets and KD were searched in the PubMed database and Google Scholar. Articles published in the last decade were included in the review. The search was conducted with the

following keywords: ketogenic diet, safety, obesity, health, mortality.

The Essence of KD

KD is an alternative diet with fat as the primary energy source. According to current recommendations on healthy eating, carbohydrates should provide 45-60% of all calories, protein - 10-20%, and fat - up to 30% (3). In KD, this ratio is quite different: carbohydrates – 5% (up to 20%), proteins - 10%, fats - 70-85% (Table 1) (4,5). If the recommended daily energy intake of an individual is about 2000 kcal, then at KD his portion should bring in approximately 165 g of fat, 75 g of protein and only 20 g of carbohydrates. The abundance of fat can be ensured both from vegetable sources (olive oil, avocado, coconut, palm, linseed, etc.) and animal products (fatty meat, organ meat, sausages, lard, bacon, butter, poultry fat, fatty fish and others).

A strict restriction on carbohydrates is achieved by excluding foods naturally rich in sugars from the menu:

- ◇ fruits (only berries are allowed, in very small quantities)
- ◇ starchy vegetables (carrots, turnips, potatoes, etc.)
- ◇ legumes
- ◇ cereals and pasta of all kinds
- ◇ milk (source of milk sugar - lactose)
- ◇ desserts (incl. containing sweeteners)
- ◇ alcohol

Nuts and a variety of vegetables (tomatoes, onions, garlic, etc.) are restricted.

Currently, KDs are most commonly used by elite athletes and bodybuilders aiming to reduce their body fat rapidly, as well as by people with metabolic disorders, overweight or obesity.

Biochemical Basis of KD

In the course of its long evolution, the human body has adapted to use glucose as a major energy source. Many of our tissues can function by using fatty acids (e.g. muscles), but there are also glucose-dependent organs and cells. This is especially true of the brain, kidneys, and erythrocytes. The human brain needs an average of 120 grams of glucose per day. In acute carbohydrate restriction, the brain relies on glycogen stores. However, they run out quickly - within 1-3 days. To ensure the normal function of the brain, which controls all other organs, the body triggers a process called gluconeogenesis (i.e., synthesis of glucose in the body from non-carbohydrate sources - fatty acids or amino acids, i.e. proteins). For the first few days (3-5 days) after carbohydrate fasting, the blood sugar level (respectively, providing the brain with glucose) is maintained at the expense of protein degradation, i.e. of muscle mass. However, it is very disadvantageous for the human body to synthesize glucose from a protein and to lose valuable muscle tissue. Metabolic adaptation to preserve muscle mass storage is turning to ketogenesis from fat (6,7,8). This process allows a large part of the body's energy expenditure to be covered by the ketone bodies (ketones) obtained from the breakdown of fat stores (adipose tissue). Ketones are water-soluble molecules produced in the liver by fatty acids. In carbohydrate starvation, they cover part of the brain's energy needs. When the blood ketones reach a concentration >2 mmol/L a condition known as ketosis occurs. In ketosis, the body relies primarily on fat as an energy source. Ketogenesis arose during the evolution due to episodic starvation in the nomadic period of human history. The enzyme that breaks down fat into free fatty acids and ketones is called hormone-sensitive lipase, and is only active if insulin levels are low. This means that the import of carbohydrates must stop in order to start ketogenesis. A healthy person often falls into ketosis spontaneously - e.g. after prolonged sleep (because he did not eat), after heavy training or exercise without nutritional support, after prolonged fasting on various occasions, etc. Plasma concentrations of ketones at various conditions are presented in Table 2.

Table 2. Concentration of ketone bodies in the blood in various physiological and pathological conditions, adapted from (6,7,8).

	Plasma ketone concentration (mmol / L)
Mixed Eating	0.1
Fasting 2-3 days	1.0
Fasting for 1 week	5
Ketogenic diet	5-6
Fasting for 3-4 weeks	6-8
Ketoacidosis	8+
Diabetic ketoacidosis	Up to 25

How Do Ketones Work?

Because they are relatively small and water-soluble molecules, ketones cross the blood-brain barrier and reach two very important centres in the cerebral cortex: the centre of appetite and the centre of euphoria. In this way, ketones affect the levels of the hormones ghrelin and leptin (regulators of appetite and satiety). They suppress appetite, improve hunger control and reduce cravings for sugary foods. As a result, energy intake and body weight are reduced without significantly affecting muscle mass.

Effect of KD on Overweight and Obesity

Currently, KDs are uncontrollably used for overweight and obese people without considering the health risks of carbohydrate starvation. There is no evidence yet that, in the long run, KDs are easier to follow and more successful than other alternative eating patterns in overweight people (9). KDs may be an option for some people who have had difficulties losing weight with other methods. However, the exact ratio of fats, proteins, and carbohydrates that are needed to achieve the goals are different in different individuals due to their unique genome and body composition. A meta-analysis of 13 randomized controlled trials (lasting >12 months) compares two isocaloric diets - KD (very low carbohydrate diet) and a low-fat diet. The results are similar - the average weight loss with KD is only 2 pounds more over a 12-month period. In the second year, the results are countervailed (10). An analysis of 26 short-term studies (4-12 weeks) compares appetite control by KD and a low-fat diet (isocaloric), before and after

the nutritional intervention. The results are similar in terms of appetite and weight loss (11).

Safety Profile of KD

A number of common side effects due to **extreme restriction of CHs** have been described: fatigue (mental and muscular), muscle cramps, nausea, dizziness, dysthymia (apathy, depression, aggression), irritability, headache, cognitive impairment (disorders of memory, concentration, brain fog), constipation and more (12,13,14,15).

A number of studies have looked at the relationship between CH intake and overall mortality. One of the most extensive studies in this area is ARIC (Atherosclerosis Risk in Communities) (16,17). It investigates the link between average CH consumption and the risk of death over a 25-year period. Eating habits of 15428 people aged 45-64 years, all without extreme cases of daily energy intake (within 600 - 4200 kcal for men and 500 - 3600 kcal for women), have been studied. After adjusting for risk factors (age, gender, ethnicity, BMI, energy intake, education, physical activity, income, smoking, diabetes mellitus, etc.), the results show a statistically significant, non-linear U-shaped relationship ($p < 0.001$) between risk from death and eating CH. The lowest risk is observed when the consumption of CHs is providing 50-55% of daily energy intake. Mortality is highest when CH consumption is less than 30% and gradually increases when CH consumption exceeds 60%. A relatively higher risk of death was found when CHs on the menu were replaced with animal fats and protein, and lower when replaced with vegetable fats. The conclusion is that there are significant differences in the average predicted life expectancy based on CH intake. A meta-analysis including 12 publications of studies in North America, Europe, Asia, as well as international cohorts in recent years (including a total of 432 179 people and 40 181 deaths - 9.3% of the total group followed) confirms ARIC results (18,19,20,21,22,23,24,25).

The most significant health risks in strict compliance with KD are:

- ✧ in children: slow growth (26), frequent acidosis, increased incidence of infections (by 2-4%, due to impaired neutrophil function) (27);

- ✧ problems with the gastrointestinal tract: bad breath (due to ketonaemia), reflux, biliary dyskinesia, constipation, pancreatitis, etc.
- ✧ in some human populations, due to genetic polymorphism, there is a reduced tolerance to high fat intake with the consequence of greatly elevated triglycerides and cholesterol (dyslipidaemia) and increased cardiovascular risk (19,22)
- ✧ worsening and exacerbation of kidney diseases (renal failure, gout, etc.), liver conditions, bone problems (including fracture healing and osteoporosis, (28);
- ✧ tendency for hypoglycaemia
- ✧ electrolyte imbalance affecting potassium, calcium, and magnesium, which is manifested by painful cramps, nausea, dizziness

It is absolutely contraindicated for KD to be followed by children and adolescents; women during pregnancy and lactation, women with secondary amenorrhea and reproductive problems; individuals with BMI <25; individuals with eating disorders (anorexia, bulimia, etc.), with alcoholism or other addictions; mental illness (psychosis); porphyria and some congenital enzyme deficits; renal or hepatic insufficiency (including active chronic hepatitis), gout; some endocrine disorders: type 1 diabetes, hyperthyroidism, Cushing's syndrome; haematological diseases; fresh myocardial infarction (6 months ago), unstable angina, heart failure, vascular incident; progressive inflammatory and malignant diseases (29,30,31,32). **Relative contraindications to KD** are kidney and gall bladder stones and treatment with diuretics (risk of developing hypokalaemia and heart rhythm disorders).

Several issues of increased difficulty are raised in relation to following a KD. First of all, is the risk for long-term health and safety (over 1 year). Another serious question is whether the side effects do or do not outweigh the potential benefits in polymorphic patients. Obese individuals have a number of accompanying disorders, some of which can worsen and exacerbate during ketosis. There is a serious risk of following a KD in patients with disorders of protein and lipid metabolism (kidney, liver, pancreatic) and induction into ketosis in these patients can be life-threatening. Last but not least is the question

of the selection of fat sources in KD and the fatty acid profile of the food. It is very important whether 70–80% of the calories in the daily menu will come from mostly saturated fat or at the expense of monounsaturated and polyunsaturated fat. With the development of nutrigenomics and nutrigenetics, it has become clear that there is a genetic polymorphism in the human population regarding the metabolism of various fatty acids with unpredictable consequences for atherogenic risk.

Instead of a Recommendation

When switching to KD, it is advisable to choose, as a matter of priority, foods containing mostly unsaturated fats: fish, nuts, seeds, olive oil, avocado, and poultry. It is desirable to avoid sources of saturated fatty acids, especially unconventional for the geographic area such as coconut and palm oils. It is absolutely inappropriate and dangerous for health to include hydrogenated oils rich in trans-isomers of fatty acids. A healthier alternative to classic KD as a weight loss approach could be to replace CHs with mostly vegetable fats and proteins. This eating pattern can be considered as a long-term strategy to achieve active longevity and preserved health (33). KD may be an alternative for some people who have had difficulty achieving their health or weight goals through other methods. However, the exact ratio of fat, CH and protein will vary from one individual to another due to the specific set of genes and features in body composition. Therefore, if a person decides to start KD, it is recommended that they consult a dietician to monitor any biochemical changes after starting the diet. The doctor will create a nutritional plan that is tailored to the health status and physiological characteristics and will give adequate instructions for reintroducing the carbohydrates (in the appropriate quantitative and qualitative composition) after reaching the goals. This will minimize the health risks of prolonged ketosis. Potential side effects of KD can be limited by monitoring the patient during the initiation and maintenance of KD (34). The side effects of KD are manageable, however, it is important for the clinician to recognize them and to make changes of nutrition and health assessment. The diet could have/has a therapeutic potential on different diseases in clinical practice. The present

review also questions the side effects when the diet is not under medical supervision.

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