Ketogenic diet in epilepsy: an updated review

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SUMMARY
Introduction. Finding an effective epilepsy treatment has been a challenge in medicine for centuries. It is especially difficult to treat drug-resistant epilepsy, which accounts for 20–30% of epilepsy cases, even after the introduction of numerous new anti-epileptic drugs (AEDs). This gives an incentive to search for therapies other than pharmacotherapy, e.g. the ketogenic diet (KD).

Aim. The present review paper aims to present the current state of knowledge regarding the effectiveness of the KD, its mechanism of action, indications, method of treatment and potential adverse effects.

Material and method. The review covers relevant most recent (up to March 2018) papers using PubMed and Medline databases.

Results and discussion. The history of the KD dates back to ancient times. It was believed to be very promising at the beginning of the last century, but then was temporarily ‘forgotten’ and has been undergoing a second renaissance since around 1990. It is currently recognised in most countries. The KD is administered mainly to children but over the last few years there have been attempts to use it in adults as well. The theoretical basis of the diet consists in the fact that it ‘mimics’ the metabolic state of an organism subject to fasting by replacing the basic source of energy for the brain, that is glucose, with ketone bodies, which are a product of fat breakdown. In spite of scientific progress, the exact mechanism underlying the KD is still not known. Its effectiveness, at first mainly as an add-on therapy, and in some cases as the first-line monotherapy, is rated quite highly (>50% seizure reduction in >50% patients; of which in 20–30% of patients seizures are reduced by >90%). It can be used to treat all types of epileptic seizures after excluding contraindications. The KD, like any medical therapy for serious illnesses, may cause adverse effects. Most of them are mild, can be prevented, and if they occur, can be fairly easily treated

Conclusion. The KD as add-on therapy or as monotherapy is a medical treatment of epilepsy administered under medical supervision.

Key words: ketogenic diet • epilepsy

INTRODUCTION
Epilepsy is one of the most common disorders of the nervous system. It is a health problem as well as a social and economic one. Approximately 50 million people around the world suffer from epilepsy, with around 3.4 million of them in Europe. Every year 2 million new cases are diagnosed. The incidence in children is roughly of 5–7 per 100 000 per year, whereas the prevalence is of 20–60 per 100 000 (Rezaei et al., 2017; Kinderen et al., 2011). In spite of significant progress in pharmacotherapy, the percentage of non-responding patients has remained unchanged. The new generation AEDs, undoubtedly better tolerated and generally safer, have not, unfortunately, proved significantly more effective against epileptic seizures than the classical medicines (Hartman, Vining, 2007). Normally, the first administered AEDs leads to freedom from seizures in 50% of
patients, the second in around 11%, the third in around 3%, whereas all subsequent AEDs work in only 0.8% of patients (Mohanraj, Brodie, 2006). Still only around 60% of patients are completely free from seizures or achieve substantial control, whereas 30% are refractory to this form of therapy. Patients who suffer from seizures in spite of the administration of two subsequent, appropriately-selected AEDs that are well applied and tolerated, are diagnosed with refractory epilepsy (Kwan et al., 2010). Seizures persisting despite treatment may cause developmental delay in children, cognitive impairment, poor life quality of the patient and their family or even sudden death. A diagnosis of refractory epilepsy forces the physician to resort to therapies other than pharmacological: resective surgery, vagus nerve stimulator (VNS), depth electrode stimulation or the ketogenic diet (KD). In patients whose seizures are related to a localised epileptic focus, neurosurgery is considered the first-line treatment. In patients who do not qualify for neurosurgery, VNS implant or the KD are considered. Compared to VNS, the KD is easier to use and its potential anticonvulsant effect is observed earlier – usually after just 2–4 weeks (in the case of VNS it takes several months) (Kossoff et al., 2009b).

The KD is recognised all over the world; it is used in more than 60 countries. It is characterised by high fat content, protein content appropriate for age and low carbohydrate content. In the KD, a so-called ‘ketogenic ratio’ is determined (4:1, 3:1, 2:1), i.e. a weight ratio of grams of fat to grams of protein and carbohydrates combined (respectively 4, 3 or 2 g of fat for 1 g of proteins and carbohydrates combined) (Kossoff et al., 2009a). Over the last few years, interest in this therapy has been increasing both in epilepsy centres and among parents of underage patients as well as in adult patients. The number of publications on the KD has been growing rapidly. In the years 1991–1999, from 5 to 34 papers per year were added to the PubMed database; in the years 2000–2010 it was between 34 and 125; in 2011–2017 the number of publications per year exceeded 150. In 2017 as many as 282 publications on the KD appeared in PubMed. More in-depth knowledge of the mechanism of action, indications and less restrictive versions of the KD is acquired. In 2012 in the United Kingdom, NICE (National Institute of Health and Clinical Excellence) advised in its recommendations that KD be considered for use in children who had failed to respond to appropriate pharmacotherapy administered so far (Nunes et al., 2012).

AIM
The present review aims to present the current state of knowledge regarding the effectiveness of the KD, its mechanism of action, indications, method of treatment and potential adverse effects.

MATERIAL AND METHOD
The review includes 175 relevant and most recent (up to March 2018) publications identified using PubMed and Medline databases.

RESULTS AND DISCUSSION

History of ketogenic diets
The history of the KD is very long, dating back to antiquity and biblical times. Fasting was observed to have a beneficial effect on reducing devastating seizures which was reported in the works of Hippocrates (5th century B.C.) and in the Gospel according to Mark. Interest in the dietary treatment of epilepsy was revived at the beginning of the 20th century, a time when phenobarbital (PB) and bromides were the only available AEDs. French physicians Guelpa and Marie (1911) were the first to describe the impact of fasting on reducing seizure intensity. In the United States, an osteopathic physician Conclin and Macfadden (1922) wrote the first reports regarding the beneficial effect of fasting on epileptic seizures. In 1921, during an American Medical Association (AMA) convention, Rawle Geyelin presented observations of a group of 30 patients aged 3.5–35 years, that fasted for 20 days and which led to absolute seizure freedom in 87% of patients. Woodyatt (1921), having used the diet in diabetic patients, drew attention to the presence of acetone and beta-hydroxybutyric acid (BHBA) in the blood of both healthy people subject to fasting and those on a low carbohydrate and high fat diet. At the same time Wilder (1921), having used the diet in diabetic patients, drew attention to the presence of acetone and beta-hydroxybutyric acid (BHBA) in the blood of both healthy people subject to fasting and those on a low carbohydrate and high fat diet. At the same time Wilder (1921) and then Peterman (1925) from the Mayo Clinic presented a proposal of a diet in which most of the energy came from fat and the metabolic processes arising while on the diet mimicked the metabolic state achieved during fasting. Due to the fact that the diet induced the state of ketosis, which likely plays a role in fighting epileptic seizures, this diet was named the KD. General rules for its application have not changed till this day (Wheless, 2008). By 1930, the KD had been used in 272 children in the USA (A.D.B., 1931) as monotherapy or, in some patients, with added phenobarbital. In 1938, the introduction of phenytoin (PHT), expected to be more effec-
tive and easier to use than the diet, perceived as a difficult therapy, hampered its wider spreading. More AEDs were successively introduced (since the 1950s – 26 in total) (Elia et al., 2017) and they have raised hopes for complete seizure control; however, around 30% of patients still do not reap the expected benefits of pharmacotherapy. In the 1980s the diet was taken up once more by professor Freeman and his co-workers from Johns Hopkins Hospital in Baltimore, USA, in a limited number of patients (around 10 a year). As a result, in 1992 they published a report summing up KD’s effectiveness (mostly as add-on therapy) in 58 children with epilepsy (Kinsman et al., 1992). Since the results of the first multi-centre studies – evaluating the efficacy of the KD – were presented at the American Epilepsy Society (1996), interest in this therapeutic method has been growing (number of reports from ca. 100/year in the nineties to over 200 in 2017). The principles for using the KD in children were published in 2009 (Kossoff et al., 2009a). As more insight is gained into its mechanism of action, the KD is increasingly being used in diseases other than epilepsy (Stafstrom, Rho, 2012).

Mechanism of action of the ketogenic diets

Though there is no doubt as to the efficacy of the KD in refractory epilepsy treatment, its precise mechanism of action remains unknown. In the case of pharmacotherapy, in contrast, the mechanisms of many AEDs are known (e.g. through voltage-dependent sodium channels), which might suggest their potential efficacy in epilepsy treatment; nevertheless, it has not brought about a decrease in the percentage of patients with refractory epilepsy, the underlying mechanism of which cannot be entirely explained either (Rho, Stafstrom, 2012). Given the fact that the KD is effective in many types of epilepsy, it must be acknowledged that its mechanism of action is undoubtedly very complex. During fasting, or when the carbohydrate supply is lowered and the fat supply simultaneously increased, large amounts of free fatty acids (FFA), unable to pass the blood-brain barrier, appear in blood. In liver mitochondria, in the beta-oxidation process, they are converted via acetyl-CoA into ketone bodies: acetone, acetoacetate, and β-hydroxybutyric acid. They are subsequently released into the circulatory system, from where they easily cross the blood-brain barrier. During the application of the KD, the metabolic status accompanying fasting is ‘mimicked’ which means that the cells of many organs, especially of the central nervous system, use fat breakdown products, i.e. ketone bodies, as their main source of energy replacing glucose. The ketone bodies, instead of glucose, become the source of acetyl-CoA for the Krebs cycle. This is a key process for the KD’s action. Moreover, the ketones constitute an essential building block in the process of biosynthesis of cell membranes in the developing brain. As the efficacy of the KD in epileptic seizure reduction is proven, it is clear that the KD impacts on neuronal excitability (Bough, Rho, 2007). Multiple reports indicate that its mechanism of action is particular and different from epilepsy therapies used so far (Rogawski et al., 2016). Among recognised mechanisms of the KD’s action, emphasis is put on the role of caloric restriction, decreased glucose supply and glycolysis reduction, as well as on the direct impact of ketone bodies and free fatty acids (including PUFAs – polyunsaturated fatty acids) on triggering a series of complex biochemical, hormonal and even genetic processes (Masino, Rho, 2012; Danial et al., 2013; Rogawski et al., 2016). Ketone bodies, free fatty acids and limited glucose supply influence both directly and indirectly epileptic seizure control through diverse mechanisms. Available studies indicate that in order to achieve a full anticonvulsant effect, co-occurrence of all three factors above is necessary (Bough, Rho, 2007). For the KD’s action, it is essential to decrease the glucose supply, reduce glycolysis and elevate the blood level of ketone bodies, which represent an alternative ‘fuel’ for cells. In the process of anaplerosis (replenishing missing intermediates participating in the Krebs cycle – TCA) they supply the Krebs cycle, responsible for generating energy (ATP) and indirectly responsible for neurotransmitter production (Rogawski et al., 2016). That reduced glucose and elevated fatty acids cause chronic ketosis – which triggers a series of complex biochemical, hormonal or even genetic processes – has been confirmed. Activation of these processes affects the stabilisation and/or stimulation of cellular metabolism. As a result, it inhibits neuronal dysfunctions accompanying convulsant activity. The scope of the present paper does not allow for a detailed presentation of the numerous interdependent elements (established so far or currently being investigated) that determine the final, indisputably-confirmed effect of the KD on epileptic seizure reduction. The most important ones are, however, worth mentioning. The impact of the KD on mitochondrial function is obvious. It consists in increased biogenesis of these cell organelles, elevated production of energy carrier molecules (ATP).
inside them, leading eventually to the build-up of energy reserves in cells. In this process, an essential role is played by PUFAs boosting UCPs (uncoupling proteins) that stimulate mitochondria to produce more energy (Bough et al., 2006). Energy production in cells is conditioned by NAD (nicotinamide adenine dinucleotide). The latest reports point to a probable increase in the NAD+/NADH ratio as a key factor in the KD’s action (Elamin et al., 2017). Moreover, the KD helps to reduce oxidation stress in neurons. Enhanced expression of UCPs induces decreased mitochondrial membrane potential, and consequently reduced ROS (reactive oxygen species) production. A rise in energy production in mitochondria and a drop in the number of free radicals contribute to the prevention of neuronal dysfunction, convulsions or even neurodegeneration (Bough et al., 2006; Greco et al., 2016). Furthermore, reduced glucose and the state of ketosis cause the activation of ATP-sensitive potassium channels (KATP) in neurons which results in reducing their convulsant excitability (Bough, Rho, 2007; Masino, Rho, 2012). The KD also causes changes in metabolism and in the release of neurotransmitters. The synthesis of the inhibiting neurotransmitter GABA is increased, while its breakdown slows down, thus increasing its levels in the cerebrospinal fluid. Besides this, ketosis (BHBA and acetoacetate) directly triggers a decrease in presynaptic release of the excitatory neurotransmitter – glutamate which directly leads to the inhibition of excitatory glutamate-dependent synaptic transmission (Bough, Rho, 2007; Masino, Rho, 2012; Danial et al., 2013; Kossoff, Wang, 2013). Increased concentration of norepinephrine and adenosine, related to restricted glucose supply, is also crucial for the anticonvulsant effect of the KD. Through activation of adenosine A1 receptors, adenosine impacts the ATP-dependent potassium channels mentioned above (Masino, Rho, 2012). Among many aspects unpinning the KD’s action, one that has been recently stressed is the increase in the leptin level. Leptin is an endogenous peptide causing a decrease in synaptic excitability (Rho, Stafstrom, 2012). Attention should be paid to the specific role of PUFAs in the twofold reduction in neuronal excitability, directly and indirectly achieved through the activation of fatty acid receptors, PPARs (peroxisome proliferator-activated receptors) in particular (Bough, Rho, 2007; Masino, Rho, 2012; Kossoff, Wang, 2013).

Many authors emphasise the KD’s influence on inhibiting the mTOR (mammalian target of rapamycin) pathway in the brain (its hyperactivity has a convulsant effect and conduces to epileptogenesis), this is yet another way in which the KD produces an anticonvulsant and antiepileptic effect (McDaniel et al., 2011; Danial et al., 2013; Kossof, Wang, 2013). Ketones (KBs) and their metabolic intermediates (acetyl-CoA, aspartate, PUFAs), among other effects, have a strong influence on the expression of genes linked to cellular metabolism and ROS resistance (Youngson et al., 2017). The period of around 2 weeks that is needed to reveal the anticonvulsant effect of the KD correlates with the time required for alterations to gene expression, mitochondrial proliferation and uncoupled proteins’ upregulation (Maalouf et al., 2009). During treatment with the KD, the glucose level in the blood remains correct, despite its minimum intake when on the diet, owing to the fact that it is produced via gluconeogenesis from amino acids and glycerol released from triglycerides in the beta oxidation process. Thanks to that cells that absolutely require glucose, such as red blood cells, devoid of mitochondria, can satisfy their metabolic needs (Walczak, Wick, 2017). The KD probably also affects the gut microbiome’s composition by increasing the quantity of bacteria producing short-chain fatty acids (SCFAs), which then pass from the bloodstream into the brain, where they are one of the factors impacting the regulation of seizure activity (Newell et al., 2016). Until recently it was believed that, due to the limited ability of ketones to cross the blood-brain barrier in adults, the KD could not be used in this age group. This assumption has turned out to be incorrect. It has been proven that in disease-related stress, the number of proteins transporting ketones (MCT – monocarboxylic acid transporters) to the brain increases (Azevedo de Lima et al., 2014). This is evidenced by the growing number of reports on the KD’s effectiveness in the treatment of adult epilepsy.

In summary, the processes described above, as well as some others not mentioned in the present paper, produce the following results: an increase in neuronal energy reserves (increased mitochondrial biogenesis, increased production of ATP), improved mitochondrial function, a reduction in oxidative stress leading to neuronal damage provoked by ROS and reactive nitrogen species (RNS), the modification of neuronal circuits and cell properties towards reinforcement and normalisation of neuronal function, stabilisation of cell membranes, alteration to the excitability and plasticity of neurons, and the attenuation of inflammatory reac-
tions in nervous tissue. Although the exact mechanism of action of the KD has not been entirely understood, it has been assumed on the basis of previous studies that ketones alter the metabolism of neurons, affect the level of neurotransmitters and regulate the development of neurons (Zhang et al., 2018). KD therapy combines numerous beneficial mechanisms of action, contributing to success in the treatment of epilepsy not only by inhibiting epileptic seizures but also by affecting the course of epilepsy (Boison, 2017). Ultimately, this complex mechanism leads not only to the already known anticonvulsant action of the KD but also produces its neuroprotective, anti-inflammatory and epileptogenesis-inhibiting effects (hence the long-lasting anticonvulsant effect persisting after discontinuation of the treatment) (Maalouf et al., 2009; Danial et al., 2013; Masino, Rho, 2012; French et al., 2017; Chorągiewicz et al., 2010). The clinical effect of the KD cannot be explained with reference to only one mechanism of action because, as in the case of AEDs, it is multifaceted and caused by many factors. Even though the AEDs lead to seizure control in many patients, unfortunately not all patients become seizure-free through pharmacotherapy. The KD makes it possible to control seizures in patients with refractory epilepsy. The therapeutic effect of the KD results from its impact on the metabolism and is completely different from the mechanism of action of the AEDs. Studies on the KD may bring about entirely new therapeutic strategies in refractory epilepsy. Further research on the KD mechanism is necessary (Rogawski et al., 2016).

The KD in epilepsy – evaluation of effectiveness
Many epileptologists consider the KD to be one of the most effective treatments for paediatric epilepsy as add-on therapy, but sometimes as monotherapy (even for first-line therapy in some situations), apart from resective neurosurgery (in cases where neurosurgery is indicated) (Kossoff et al., 2009b).

Case studies
Hundreds of papers published over the last 30 years present similar results: in patients on the KD, following treatment for 3–12 months, a >50% reduction in seizures (as compared to the period preceding the diet) is observed in >50% (24–83%) of patients treated with the KD, and in 30% (30–46%) of those patients seizures decrease by >90%, while 10–18% become entirely seizure-free (Vining et al., 1998; Henderson et al., 2006; Keene, 2006; Neal et al., 2008; Li et al., 2013b; Martin et al., 2016). In 1998, Freeman et al. published observations of 150 patients after 3, 6 and 12 months of KD treatment in whom they achieved the same results. In 2001, the same authors published a paper assessing the results of treatment in this group of 150 patients 3 and 6 years after its initiation. 13% of patients remained seizure-free, whereas in 14% seizures had been reduced by 90–99%. In 29 patients it had been possible to discontinue the AEDs, while 28 patients were taking only 1 AED. Fifteen patients continued the KD (Hemmingway et al., 2001).

Meta-analyses
Since 2000, several meta-analyses evaluating the effectiveness of the KD, based on retrospective and prospective studies, have been published. All presented the same results. They indicated a seizure reduction of >90% in about one third of patients; >50% in 30–50% of patients and complete freedom from seizures in 15–16% of patients (Lefevre, Aronson, 2000; Levy, Cooper, 2003; Henderson et al., 2006; Keene, 2006). All of the above meta-analyses pointed to the lack of randomised controlled trials (RCTs) trials among the papers assessed and highlighted the necessity of undertaking RCTs in larger groups of patients. They concluded that, in spite of the lack of such trials, the results obtained were sufficient to rate the KD as effective in treating seizures in children with intractable epilepsy.

Controlled studies
The first RCT was undertaken in London and published in 2008 (Neal et al., 2008). Children were randomly assigned to a group receiving the KD after 1 month of initial observation (54 patients) and a control group (49 patients) who started receiving the diet after 4 months. In the course of the 3-month observation period the first group experienced seizure reduction of >50% in 38% of patients, whereas in the control group only 6% of patients (p < 0.0001) experienced such a decrease. Reduction of seizures by >90% was observed in 7% and 0% of patients respectively (p = 0.0582).

The following year, the first and so far the only blind-ed crossover study was published. It concerned children with Lennox-Gastaut syndrome. The patients were randomised into two groups: the first group received fluids sweetened with saccharin (experimental group), the second received fluids sweetened with glucose (placebo). The results, even if statistically insignificant (P = 0.07),
indicated a more substantial seizure reduction in children in the experimental group (receiving saccharine) (Freeman et al., 2009). Due to methodological difficulties it is practically impossible to conduct a blinded crossover study on patients receiving the KD.

Recently numerous RCT evaluating the treatment of intractable epilepsy in children via the use of the KD were published. It is worth discussing some of them. Comparisons of the KD’s efficacy were conducted taking into account the following parameters: the efficacy of the KD initiated with or without fasting, without significant differences found (Bergqvist et al., 2005), the effect of the KD at a 4:1 ratio and at a 3:1 ratio – with better seizure control at the 4:1 ratio (Seo et al., 2007), the modified Atkins diet (MAD) with the use of 10g of carbohydrates a day as compared to the group receiving 20g a day with better results in the first group (Kossoff et al., 2007), children treated with the classic KD at both the 2.5:1 and 4:1 ratio; less adverse effects were noticed at the lower ratio (Raju et al., 2011). El-Rashidy compared children receiving the classic KD at the 4:1 ratio and the MAD to children who continued to receive their pharmacological treatment applied so far, and the best anticonvulsant effect was achieved in the children on the 4:1 KD (second best in patients on MAD) (El-Rashidy et al., 2013). A significantly higher effectiveness of MAD as compared to traditional treatment (care as usual – CAU) was noted by Sharma et al. (2013). In 2016, a meta-analysis taking into account the above-mentioned RCT studies was conducted. In conclusion, its authors declared the KD to be a promising and valuable method of treatment for refractory epilepsy. At the same time they stressed the necessity of further research (Martin et al., 2016). No clear advantage of the KD over MAD was identified except in the younger children (< 2 years old) in whom the KD was more efficient at seizure reduction (Kim et al., 2016). Then Lambrechts et al. (2017) compared 26 children who received the KD to 22 who remained on CAU. The effects were assessed after 4 months. In the group treated with the KD, a >50% seizure reduction was observed in 50% of patients (including 3 patients who became seizure-free and 3 other patients whose seizures dropped by >90%). In the control group, a >50% seizure reduction was observed in only 5 patients (18.2%), including 2 seizure-free and 1 with a >90% reduction (p = 0.022).

**Distant effect of the KD**

Patel et al. (2010) evaluated the distant effect of the KD treatment in 101 patients who had discontinued the diet on average 6 years before the study was conducted (0.8–14 years). A >50% seizure reduction was maintained in 80% of patients. In accordance with the multiannual observations of numerous authors, the KD not only reduces epileptic seizures, but also has an impact on the improvement of functioning regardless of the degree of seizure control (in >80% patients), better concentration and ability to learn, improved behaviour, better sleep structure (prolonged REM phase), the possibility of AEDs reduction (in around 30% of patients) and, as a result, a visibly improved quality of life (QoL) (Pulsifer et al., 2001; Hallböök et al., 2007; Hallböök et al., 2012; Sharma, Jain, 2014; Zhu et al., 2016; Ilff et al., 2016; Bruce et al., 2017).

**Reports of EEG studies**

A beneficial effect of the KD on the EEGs has also been reported, especially on the decrease of interictal epileptiform discharges, just after 1 month of treatment. Patients in whom such a result is visible are more likely to experience seizure reduction after 3 months. Even a short treatment with the KD may cause an increase in beta activity, which suggests that the KD has an effect similar to that of AEDs with a GABAergic mechanism of action (Kessler et al., 2011). Improved background activity is also observed (Li et al., 2013a).

**When to use the KD – indications**

**Metabolic diseases with epilepsy**

Two inborn errors of metabolism related to the conversion of carbohydrates are an absolute indication for the ketogenic diet (treatment of choice): glucose transporter type 1 deficiency (GLUT1DS) and pyruvate dehydrogenase complex deficiency (PDHD). Drug resistant epileptic seizures are one of their main symptoms. Due to the difficulty of using glucose as the brain’s source of energy in these disorders, ketone bodies constitute an alternative ‘fuel’ for the brain.

The KD in GLUT1 deficiency. GLUT-1DS is a disease related to impaired transport of glucose. Decreased delivery of glucose to the brain across the blood-brain barrier by the GLUT1 transporter results in a lack of energy for the brain. The clinical symptoms include refractory seizures, early-onset encephalopathy, microcephaly, motor disorders and developmental delays. Lowered concentration of glucose in the cerebrospinal fluid (below 40 mg/dL) points to a GLUT1DS diagnosis which can be confirmed by detection of the SLC2A1
gene mutation (in 80–90% of patients). The KD is the treatment of choice in this disorder: ketones replace glucose as an energy source, thus enabling the proper functioning of nerve cells which leads to a subsidence in epileptic seizures and suppression of the progress of any developmental delay (Klepper, Leindecker, 2007). The KD should be introduced as soon as possible once the diagnosis has been made (Kossoff et al., 2009a; Lee, 2012; Elia et al., 2017).

The KD in pyruvate dehydrogenase complex deficiency (PDHD). PDHD is a rare genetically determined neurometabolic disorder, caused by impaired glucose conversion. Deficiency of the pyruvate dehydrogenase enzyme prevents the conversion of pyruvate to acetyl coenzyme-A, consequently disrupting energy production in the Krebs cycle. The KD is a treatment of choice. While on the diet there is a switch from glucose to ketones as the basic source of energy for the brain, allowing the body to ‘bypass’ the metabolic block and, consequently, prevent progressive brain damage (Wexler et al., 1997; Barañano, Hartman, 2008; Prasad et al., 2011; Lee, 2012; Sofou et al.; 2017).

**The KD in epilepsy**

**Doose syndrome.** The KD treatment is undoubtedly beneficial in Doose syndrome – *myoclonic astatic epilepsy* (MAE), which accounts for 1–2% of epilepsies below 9 years of age. Seizure reduction >50% has been observed in >50% of patients, and its complete disappearance in 30% (Caraballo et al., 2006; Kilaru, Bergqvist, 2007; Bergqvist, 2012). Stenger et al. (2017) observed the resolution of seizures after 6 months in 54% of children, while after 2 months of therapy the reduction in seizures exceeded 70% in 86% of patients. In addition, earlier introduction of KD treatment correlated with a greater improvement in cognitive function and a higher remission rate. Based on the NICE CG 137 guidelines, the KD is recommended as the first-line treatment for MAE (Nunes et al., 2012; McTague, Cross, 2013). The exceptional efficacy of the KD in MAE can be explained by the presence in some patients of mutations in the SLC2A1 gene, associated with GLUT1 DS – according to Mullen et al. (2011) in 5%. MAE may also be associated with a mutation in the SLC6A1 gene, responsible for GAT-1 dysfunction (GABA transporter protein), causing a reduction in the GABA level in the synaptic cleft, and consequently convulsions. The KD, affecting the increase in GABA concentration and its activity in neurons, applied in a patient with MAE, in whom this mutation was confirmed, led to freedom from seizures (Palmer et al., 2016).

**Early onset absence seizures.** Mutations in the SLC2A1 gene have been described by Arsov et al. (2012a) and by Thouin and Crompton (2016) in 10–12% of patients with early-onset absence seizures (below 4 years of age). In recent years, more emphasis has been put on the fact that epilepsy with generalised seizures may be the only manifestation of GLUT1 DS (Arsov et al., 2012b). Therefore, the particular efficacy of the KD in genetically determined epilepsies with generalised seizures can be explained by the presence of SLC2A1 mutation in some patients. Basically, in idiopathic epilepsies with generalised seizures, approximately 1% of patients present with the mutation in the SLC2A1 gene which sheds light on the efficacy of the KD treatment in these conditions.

**Childhood and juvenile absence epilepsy.** Groomes et al. (2011) reported a very good outcome in these patients on the KD. The likelihood of the occurrence of GLUT1 DS, as well as of other mutations responsible for the development of early epilepsy with absence seizures and other refractory idiopathic epilepsies with generalised seizures, should incline doctors to test patients for these conditions and to consider earlier and wider use of the KD in these types of epilepsy (Elia et al., 2017).

**Dravet syndrome.** Reports on the efficacy of the KD in Dravet syndrome – a severe myoclonic infantile epilepsy – have been proliferating. Numerous authors report similar results: over 60% of patients with reduction of seizures by >50% and about 10% seizure-free (Caraballo et al., 2005; Caraballo, 2011; Kang et al., 2005; Dressler et al., 2015b). Nabbout et al. (2011) demonstrated the benefits of KD equally in children with Dravet syndrome receiving stiripentol. As well as seizure reduction, the KD had a positive effect on behavioural disorders and hyperactivity.

**West syndrome, or infantile spasms (IS).** West syndrome is one of the types of epilepsy that might potentially derive the greatest benefit from the KD treatment (Kossoff et al., 2009a). Numerous reports indicate the KD’s efficacy in West syndrome refractory to pharmacotherapy. Nordli et al. (2001) was one of the first authors to present the effects of the KD on seizure reduction in children with IS. Many papers described using the KD in West syndrome in groups of patients comprising from 17 to 104 infants. A >50% reduction in seizures was observed in 60–70% of children after 3 months of treatment, in 64–72% after 6 months, and
Additionally, carers noticed the children experienced a seizure-free outcome after 1–6 months of KD treatment (Kossoff et al., 2002; Eun et al., 2006; Pires et al., 2013; Lee et al., 2013; Dressler et al., 2015a). Enhanced development was seen in 62%, EEG improvement in 35%, while in 29% a reduction in the doses of co-administered AEDs was made possible (Hong et al., 2010). Additionally, carers noticed the children experienced improved quality of life (Kayyali et al., 2014). Prezioso et al. (2018) published a review of 13 papers from the years 2005–2016 comprising in total 341 children with IS. Despite the heterogeneity of methodologies and groups of patients described, the results were comparable. On average in 35% freedom from seizures was achieved while in 60% the reduction was of >50%. The KD is considered to be a second-line treatment in refractory West syndrome (Hong et al., 2010; McTague, Cross, 2013). Some reports on its efficacy and safety as a first-line treatment have also emerged (Kossoff et al., 2008a; Hong et al., 2010; Kossoff, Wang, 2013). The KD treatment in West syndrome is usually continued for 6–8 months, while in other epilepsies it is typically applied for 2 years. (Kossoff et al., 2009b; Kang et al., 2011). If seizures in West syndrome persist after using the KD for 1 month, additional treatment should be considered (van der Louw et al., 2016). In all the reported studies, a better effect was observed in children who were older at the time of diagnosis, with a shorter seizure history and fewer AEDs previously used.

**Lennox-Gastaut syndrome (LGS).** LGS is one of the most severe childhood epilepsies. It can have different aetiologies: in 65–75% it is symptomatic (genetic-structural-metabolic), in other cases the cause of the disease remains unknown. It accounts for 1–10% of all childhood epilepsies. LGS may be considered a ‘secondary network epilepsy’ where the seizure discharges spread in the intrinsic cognitive brain network, which explains progressive intellectual deterioration accompanying the seizures (Archer et al., 2014; Asadi-Pooya, 2018). Treating this group of patients requires a particular challenge and its long-term outcome is often unsatisfactory (Mastrangelo, 2017). In 2012, Lemmon et al. conducted a retrospective evaluation of the KD’s efficacy in 71 children with LGS. In 51% of children seizures were reduced by >50% after 6 months, in 23% by >90%, and 1% remained seizure-free. The results after 12 months were similar. Caraballo et al. (2014), Zhang et al. (2016) and Sharma et al. (2015) obtained even better results in children with LGS. In addition, the authors proved that the improvement in background EEG activity and the decrease in interictal epileptiform discharges after the introduction of the KD correlates with better seizure control and may be a prognostic factor for therapeutic efficacy in patients with LGS. In the treatment algorithm for LGS, elaborated by Cross et al. (2017), the KD found a place next to pharmacotherapy and neurosurgery. The authors suggest using this method in some patients relatively early, once the first-line medicines (valproic acid [VPA] + lamotrigine [LTG]) have failed, even before introducing rufinamide (RFN). The rapid response to treatment with the KD (within 3 months) in children in whom it is going to be effective is an indication that the KD should be tried early in LGS therapy.

**Super refractory status epilepticus (SRSE).** In recent years, there has been a ‘revolutionary’ change in the approach taken regarding the use of KD in urgent situations and especially in SRSE. We can classify a case as SRSE if it persists after 24 hours of intensive anaesthetic treatment has been initiated or if it recurs after this time during attempts to discontinue treatment (Appavu et al., 2016). Reports confirming the effectiveness of the KD in the treatment of SRSE have been appearing in print since 2008. Kossoff and Nabbout (2013) analysed 10 publications (2008–2012), describing a total of 32 cases of children and adults, in whom SRSE had a different aetiology and different variants of the KD were used. In 41% of patients, SRSE was caused by autoimmune or inflammatory diseases accompanied by fever (encephalitis, Rasmussen syndrome). In this group fever induced refractory epileptic encephalopathy (FIRES) in school age children was also diagnosed. The KD in SRSE was introduced after at least 24 hours of ineffective pharmacotherapy. A disappearance of the seizures was observed in 40–100% (78% on average) of treated patients and occurred within 1–19 days (average 7.0) (Kossoff, Nabbout, 2013; Appau et al., 2016; Farias-Moeller et al., 2017). In emergency situations such as SE, or in patients already receiving the KD, if enteral feeding is impossible (e.g. due to ileus or other serious gastrointestinal disorders), it is possible to use the parenteral route (intravenous) as an emergency solution (Strzelczyk et al., 2013; Farias-Moeller et al., 2017; Dressler et al., 2018). An opinion on the effectiveness of the KD in new-onset refractory status epilepticus (NORSE) and in the course of FIRES was presented at the first international symposium on these diseases (Gaspard et al., 2018). Further research on the optimal
use of the KD in SE is needed (e.g. when and how should it be introduced? How long should it continue?). In the case of refractory status epilepticus, effective treatment with the KD can directly save lives (Kossoff, Nabbout, 2013; Dulac, Takahashi, 2013). FIRES is a type of epilepsy that often poorly responds to treatment, with an epileptic status and fever at the onset, in previously healthy school-age children, in whom neuroinfection has been excluded, and is likely to cause progressive developmental disorders. The KD may be the only effective therapeutic option in these cases (Nabbout et al., 2010, Kramer et al., 2011; van Baalen et al., 2017).

**Tuberous sclerosis complex (TSC).** The KD in TSC treatment deserves special consideration. It is an acknowledged fact that hyperactivity of the mTOR pathway plays an important role in the pathogenesis of TSC (and probably also in other epilepsy syndromes, by promoting epileptogenesis). It is also recognised that one of the mechanisms at work in the KD consists in hindering this process (Mc Daniel et al., 2011; Danial et al., 2013). The epilepsy in TSC is highlighted as a condition in which the use of the KD is particularly beneficial (Kossoff et al., 2005; Kossoff et al., 2009a; Park et al., 2017). As a third-line treatment, it is recommended in IS in the course of TSC, especially in children who cannot undergo neurosurgical treatment (Curatolo et al., 2012).

**Epilepsies with other etiologies.** Epilepsy with a different etiology may also respond unexpectedly well to the KD treatment. The positive result of KD treatment in epilepsy caused by hypoxic-ischemic encephalopathy was observed by Thammongkol et al. (2012): a reduction in seizures exceeding 50% after 3 months in 4 out of 8 children, maintained in 3 out of the 4 that remained on the diet after 12 months. Epilepsy resulting from the malformation of cortical development, including focal cortical dysplasia (FCD), accounts for approximately 50% of all refractory epilepsies in children and adults and, especially in children, constitutes the main indication for neurosurgical treatment. Despite its symptomatic character, it may respond particularly well to treatment with the KD (Jung et al. 2008; Thammongkol et al., 2012; Wang, Zhou, 2016). The KD in children with FCD probably alters disease progression by weakening the remodelling of chromatin, the main regulator of gene expression and functional cellular adaptation (Stafstrom, Rho, 2012). It is interesting to note that the best result (64.7% with >50% seizure reduction) was demonstrated in children whose malformations were due to abnormal post-migrational development compared to abnormal neuronal proliferation or abnormal neural migration (Pascal et al., 2018).

The results obtained by many authors (although only in small groups of patients so far) also indicate the effectiveness of the KD in symptomatic epilepsy caused by structural changes in the brain and suggest it is worth considering implementing the KD even in epilepsy that could potentially benefit from surgical treatment. The question of whether to apply it in all patients and at what stage of treatment (before or after neurosurgery) remains unanswered (Jung et al., 2008; Cross, 2013).

**The use of the KD in infants.** The use of the KD in infants merits particular consideration. Currently, it is believed that the KD is effective and safe also in this particular group of patients, and its use should be considered at the early stages of treatment rather than as a treatment of ‘last resort’. The effectiveness of treatment with the KD in this age group is comparable or even greater than in older children (Nordli et al., 2001; Klepper et al., 2002; Dressler et al., 2015a). Safe KD therapy in infants is possible based on ready ketogenic formulas, supplemented with necessary vitamins and microelements. In some cases, partial breastfeeding is also possible (Thiele, 2013; Dressler et al., 2015a, Wilmshurst et al., 2015a; Wilmshurst et al., 2015b; van der Louw et al., 2016, Ashrafi et al., 2017; Sampaio et al., 2017). In 2016, a group of paediatric neurologists and dietitians published guidelines on the use of the KD in infants, presenting detailed rules on the safe use of the KD in this special group of patients (van der Louw et al., 2016).

**The use of the KD in adults.** In spite of the increasing use of the KD in children, until recently there had been no interest in this treatment as a therapeutic option for refractory epilepsy in adults. However, wider use of more liberal versions of the KD – a diet based on middle-chain triglycerides (MCT), MAD and low glycaemic index diet (LGIT) – makes it easier to accept this method of epilepsy treatment in adults. Besides this, in recent years the number of children on the KD has been growing which means that ‘adult’ neurologists will need to take over their treatment at some point (Kossoff, Dorward, 2008; Cervenka et al., 2016a; Nabbout et al., 2017).

A >50% seizure reduction was reported in >40% of adult patients treated with the KD or the MAD, including the cases when the diet was used as monotherapy in newly diagnosed epilepsy (Klein et al., 2010; Cer-
A very interesting, recently published report presents the use of the KD as a non-pharmacological alternative to AEDs in two pregnant women – in one as a monotherapy and in the other combined with LTG. The diet was well-tolerated and healthy children were born at term (van der Louw et al., 2017). In general, the biggest problem in adult patients related to compliance with the strict rules of the therapy (Klein et al., 2010; Cervenka et al., 2016a; Cervenka et al., 2016b; Schoeler, Cross, 2016; van der Louw et al., 2017). The increasing demand for KD treatment of epilepsy in adult patients justifies conducting randomised trials on its efficacy and cost effectiveness in this group of patients (Martin-McGill et al., 2017).

The KD can be used in all age groups and independently of coexisting developmental disorders. In Poland, the KD has been included in the recommendations of the Polish Society of Paediatric Neurologists regarding the treatment of refractory epilepsy in children (Steinborn et al., 2017).

**Contraindications for the KD treatment**

There are a number of disorders in which the KD cannot be used. Inborn metabolic defects are the main absolute contraindications. Patients with previous fat metabolism disorders may present with serious, even life-threatening complications after receiving the KD.

The following errors of fat metabolism are the absolute contraindications to the KD:

- carnitine deficiency (primary), carnitine palmitoyltransferase (CPT) I or II deficiency, carnitine translocase deficiency
- β-oxidation defects: medium-chain acyl dehydrogenase deficiency (MCAD), long-chain acyl dehydrogenase deficiency (LCAD), short-chain acyl dehydrogenase deficiency (SCAD), long-chain 3-hydroxyacyl-CoA deficiency, medium chain 3-hydroxyacyl-CoA deficiency.

In addition, the following disorders constitute absolute contraindications to the KD: pyruvate carboxylase deficiency, porphyria, glycogen storage diseases (except type 2), prolonged QT syndrome or other cardiac diseases, liver, kidney or pancreatic insufficiency, hyperinsulinism. The conditions below are listed among relative contraindications for the KD treatment: inability to maintain adequate nutrition, surgical focus identified by neuroimaging and video EEG monitoring, parent or caregiver/patient noncompliance, and severe gastroesophageal reflux (Kossoff et al., 2009a; Kossoff, Wang, 2013; Sharma, Jain, 2014; van der Louw et al., 2016). The KD should not be used in patients with renal stones or hyperlipidaemia (Vezyroglou, Cross, 2016).

**The KD and AEDs**

There are no significant contraindications to the simultaneous use of the KD and AEDs. Usually, the diet is added to previously used medicines (except when it is used as the first-line treatment). The prospect of discontinuing medication is generally, in addition to seizure control, the main expectation of patients/caregivers. However, making changes in their administration is not recommended for at least the first 3 months. After this period, if the KD is effective, it is possible to discontinue or reduce AEDs, but there is no numerical data available. Weaning off PB and benzodiazepines is more likely to cause seizure aggravation compared to other medicines (Kossoff et al., 2009a; McArtney et al., 2017).

The influence of the KD on the absorption of AEDs may be significant due to the nausea and vomiting often observed at the beginning, as well as due to the slowed gastric emptying induced by the diet. These conditions may lead to a decreased concentration of AEDs and in consequence to a transient exacerbation of seizures. Sometimes during KD implementation, the concentration of drugs in the blood temporarily increases compared to previous levels (changes in pH, decreased protein intake, decreased urinary excretion) – in the case of PB even up to 100%. Besides that, during treatment with the KD no significant differences in the concentration of AEDs compared to the pre-diet period have been noted (Zupec-Kania et al., 2013; McArtney et al., 2017). Despite many years of combined use of AEDs and the KD, there are only a few reports available on their pharmacodynamic interaction (McArtney et al., 2017). Morrison et al. (2009) analysed a group of 115 children simultaneously treated with the KD and different AEDs: levetiracetam (LEV), LTG, PB, topiramate (TPM), VPA and zonisamide (ZNS). They stated that children receiving PB were significantly less likely to have a >50% seizure reduction than children treated with other AEDs (p = 0.003). This result, as well as the previously described potential increase in PB concentration in the blood, suggest that their simultaneous use should be avoided. The opposite effect occurred in
children treated with ZNS – the probability of a >50% seizure reduction compared to those receiving other medicines was significantly higher (p=0.04) (Morisson et al., 2009). This result may indicate a synergistic effect of the KD and ZNS. The use of the KD in combination with a VNS is another example of a synergistic interaction (Kossoff et al., 2009a).

Taking into account the huge number of patients treated simultaneously with the KD and AEDs, their mutual adverse interactions are rarely observed; however, particular attention should be paid to the concurrent use of the KD and VPA. Ballaban-Gil et al. (1998) noted that most adverse effects, including serious ones such as severe hypoproteinaemia, fatty liver disease or Fanconi syndrome, occurred in children who received VPA at the same time as the KD. This was not confirmed in later reports. Other authors did not find a significant difference in adverse effects between children receiving VPA compared to those treated with other medicines (Kang et al., 2004; Lyczkowski et al., 2005). Recently, the problem of the impact of the KD on AEDs used simultaneously has again attracted interest. Heo et al. (2017) analysed 139 patients with refractory epilepsy treated simultaneously with the KD and AEDs as a mono or polytherapy. They compared serum concentrations of AEDs (CBZ, LTG, LEV, TPM, OXC, PB, PHT, and VPA) prior to the introduction of the KD and during treatment. Important differences were found only in the case of VPA – a statistically significant (p < 0.001) decrease in concentration, and PB – an increase in concentration, although not statistically significant, which points to the need to closely monitor their levels after commencing the KD (Heo et al., 2017). Spilioti et al. (2016) observed a rapid increase in ketosis, with clinical symptoms, after discontinuation of VPA in 2 four-year-old girls with refractory epilepsy (out of 73 patients receiving the KD, combined with VPA). Stevens et al. (2016) described the case of an 18-month-old girl receiving TPM and VPA at constant doses, who presented with liver failure symptoms several days after adding the KD. Following her recovery, the KD was used again without VPA, and this time no complications were observed. This particular interaction between the KD and VPA can be put down to common metabolic pathways. VPA competes with fatty acids in the process of beta oxidation in the liver and slows their conversion into ketone bodies. During treatment with the KD, due to the lower binding capacity of proteins, the free fraction of VPA, which may exert a hepatotoxic effect, increases, but excretion of the drug is also higher (Spilioti et al., 2016; Heo et al., 2017). These facts indicate that caution should be exercised when simultaneously using the KD and VPA; additionally, blood levels should be monitored and doses changes as necessary.

It should be noted that, drugs that are carbonic anhydrase inhibitors (TPM, ZNS), as well as the KD (especially in the early phase of treatment), predispose patients to metabolic acidosis (a lowered blood concentration of bicarbonates) and also to kidney stones. Therefore, if they are used simultaneously with the KD, it is recommended to monitor the level of bicarbonates and consider their possible supplementation (Takeoka et al., 2002; Zupec-Kania et al., 2013; McArtney et al., 2017).

**Adverse effects of the ketogenic diet**

The KD, like any medical therapy for serious illnesses, may cause adverse effects. Most of them are mild, can be prevented, and if they occur, can be fairly easily treated (Kossoff et al., 2009a). In the early stages, when introducing the KD, the following adverse effects are most common: dehydration, transient hypoglycaemia (<40 mg/dl), hyperketosis, metabolic acidosis, gastrointestinal disorders (vomiting, diarrhoea, abdominal pain, constipation), anorexia, sensation of hunger, exacerbation of symptoms of gastroesophageal reflux, and lethargy. These occur despite the earlier exclusion of contraindications to the use of the KD and are not significantly related to the method of initiation (with or without fasting) although, according to some authors, they are more common in children who endure interruption in feeding, especially <2 years old. They are mainly transient and can be fairly easily remedied. Only rarely are they the reason to discontinue KD treatment (Kim et al., 2004; Kang et al., 2004; Bergquist et al., 2005; Kossoff et al., 2008b; Kossoff et al., 2009a; Luat et al., 2016; Lin et al., 2017; Cai et al., 2017).

A number of ‘distant’ adverse effects that appear only after a few weeks, months or years of treatment with the KD are also known.

**Kidney stones** may occur in 5–10% of patients (in 25% of patients treated with KD for more than 6 years). They can be prevented via adequate fluid supply and administration of citrate preparations, especially potassium citrate, which increases the excretion of citrates in the urine and reduces hypercalciuria. This action reduces the risk of nephrolithiasis to 0.9%. The risk of developing kidney stones may be slightly higher in patients receiving carbonic anhydrase inhibitors (acet-
zolamide, TPM, ZNS) (Kossoff et al., 2009a; McNally et al., 2009; Paul et al., 2010; Kossoff, Wang, 2013; Zupec-Kania et al., 2013).

Relatively often, in 14−59% (Kossoff et al., 2009a) of patients treated with the KD, dyslipidemia (hypertriglyceridermia, hypercholesterolemia) is observed. Recently, the problem of lipid profile disorders during the use of the KD – as well as their potential link with cardiovascular diseases – has generated interest amongst many authors. Zamani et al. (2016) assessed the lipid profile in the course of KD treatment in 33 children, finding a significant increase in total cholesterol, LDL and triglycerides (p < 0.001), with very good efficacy (in 63% reduction of seizures was >50%). Cervenka et al. (2016c) evaluated the impact of the MAD on the lipid profile of adult patients with refractory epilepsy. They observed an increase in total and LDL cholesterol (p = 0.01), with the correct triglyceride level after 3 months of treatment, and the absence of cardiovascular or cerebrovascular events. These values normalised naturally during the year and remained at a normal level in patients whose treatment duration even exceeded 3 years. In a prospective study on 38 patients, Azevedo de Lima et al. (2017) assessed the effect of the KD on any increase in triglycerides, total cholesterol, LDL and HDL, but also on apolipoproteins (ApoA-1 and ApoB) and a small LDL subfraction. These molecules have a particularly atherogenic effect on vascular walls. Alterations in the lipid profile in patients with refractory epilepsy result not only from the KD but also from the impact of some AEDs (CBZ, PHT, VPA) favouring ‘dyslipidemia’ by stimulation of cytochrome P450. These observations, without undermining the benefits of the KD in the treatment of drug-resistant epilepsy, indicate the need to monitor not only the classic lipid profile but also its subfractions. Dyslipidemia mostly resolves spontaneously during treatment or after interventions such as reducing the ketogenic ratio, administering carnitine, adding MCT oil to the diet or adding polyunsaturated fatty acids (PUFAs) (Kang et al., 2004; Nizamuddin et al., 2008; Kossoff et al., 2009a; Zupec-Kania et al., 2013; Yoon et al., 2013; Yoon et al., 2014; Cervenka, Kossoff, 2013; Luat et al., 2016; Ułamek-Kozioł et al., 2016; Cai et al., 2017; Azevedo de Lima et al., 2017).

The impact of the KD on the cardiovascular system’s functioning was also examined, and no significant affects were observed. The effect of dyslipidemia on the carotid intima media thickness was not confirmed after 12 months of using KD, although a decrease in its distensibility was observed compared to baseline values. This parameter normalized after 24 months (Cai et al., 2017; Luat et al., 2016). Ozdemir et al. (2016) in a prospective study of 61 children treated with the KD, did not observe any negative impact on cardiac systolic and diastolic functions. The delayed impact of the KD on the cardiovascular system requires further research.

Among the adverse effects of the KD related to the cardiovascular system, a prolonged QT interval is listed (Kang et al., 2004; Hartman, Vining, 2007; Kossoff et al., 2009a, Elia et al., 2017) as is the rare, but serious complication – cardiomyopathy. Their occurrence is associated with selenium deficiency observed during KD treatment (Kang et al., 2004, Cervenka, Kossoff, 2013). Arslan demonstrated this deficiency’s presence after 6 and 12 months of therapy in almost half (49.1%) of 110 patients assessed, however none of them was diagnosed with clinical, electrocardiographic or echocardiographic abnormalities. These results suggest the need to monitor selenium levels, and if necessary, use selenium supplements during treatment with the KD (Arslan et al., 2016). Supplementation during treatment is also required for vitamins, minerals and trace elements, insufficient in the KD, as their deficiency may be the reason for clinical disorders (Kossoff et al., 2009a; Cervenka, Kossoff, 2013; Luat et al., 2016; Cai et al., 2017).

The KD, as well as concomitantly used AEDs, especially VPA, increases the risk of carnitine deficiency, clinically manifested by weakness, decreased muscle strength, hypotonia, fatigue, apathy and also anaemia, cardiomyopathy or disorders of liver function. Hence there is a need to monitor its level in the course of treatment. Should the level of free carnitine be reduced, or clinical symptoms of its deficiency occur, supplementation must be introduced. Some authors recommend prophylactic administration of carnitine in patients on the KD (Kang et al., 2004; Kossoff et al., 2009b; Cervenka, Kossoff, 2013; Fliciński et al., 2016).

Long-term use of the KD may also lead to demineralization and increased bone fragility. Groesbeck et al. (2006) reported bone fractures in 21% of 28 children treated with the KD for more than 6 years. Bergquist et al. (2008) confirmed progressive bone mineral content loss during treatment with the KD. Besides inadequate dietary supply of calcium and vitamin D, the cause of these disorders is also associated with acidosis occurring during KD treatment, poorer nutritional status linked with chronic disease and long-term use of medication affecting the calcium-phosphate balance already
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prior to the diet. These complications can be prevented by calcium and vitamin D supplementation as well as by, during the use of the KD, avoidance/prevention of excessive metabolic acidosis (by the administration of alkalinising agents, especially if the patient receives carbonic anhydrase inhibitors). In the case of longer use of the diet, the need to periodically repeat densitometric tests (DEXA) is stressed (Kang et al., 2004; Groesbeck et al., 2006; Bergquist et al., 2008; Yuen et al., 2017). Slowed growth, observed in a relatively large number of children on the KD, even according to some authors in more than 80%, has not been entirely explained. Younger children are most exposed to this risk. Its occurrence is more likely in the presence of chronic acidosis and insufficient protein intake. Therefore, monitoring the progress of growth in children is essential, especially in those treated with the KD for a long time (Bergquist et al., 2008; Kossoff et al., 2009a; van der Louw et al., 2016; Luat et al., 2016; Cai et al., 2017).

A high-fat diet can also cause uncommon but dangerous complications such as liver dysfunction and pancreatitis. There is a risk of an increased level of transaminases (in general <200 mg/dl), sometimes already at the beginning of the treatment, a fatty liver after about 6 months and the formation of gallstones 12 months into the diet. The association of toxic liver damage with simultaneous use of VPA during the KD and also with carnitine deficiency, is stressed. These complications are usually reversible and do not require discontinuation of the diet. Patients treated with the KD should be monitored regularly in order to detect potential adverse effects on the liver (ultrasound, transaminase). If pancreatitis occurs (a very rare but life-threatening complication), discontinuation of the KD should be considered (Kang et al., 2004; Cervenka, Kossoff, 2013; Arslan et al., 2016; Stevens et al., 2016).

The increased incidence of infection, without clearly confirmed immune disorders, is mentioned among rarely described, although quite common, adverse effects associated with the KD. Generalised severe infections have been sporadically reported (Kang et al., 2004; Cervenka, Kossoff, 2013).

The KD may also be accompanied by hypoproteinaemia, occurring in about 10% of treated patients. Its cause, apart from the limited but adequate supply of protein in the diet, and increased gluconeogenesis resulting from the low supply of carbohydrates, is hard to explain (Kang et al., 2004). It can usually be compensated for by increasing the supply of protein in the diet (e.g. by reducing the ketogenic ratio). Reports on single cases of protein-losing enteropathy during KD treatment, sometimes following a difficult course, shed some light on this problem. Abdominal dynamic scintigraphy may be useful in diagnosing the cause of hypoproteinaemia occurring in the course of treatment with the KD (Moriyama et al., 2015; Ahn et al., 2017). Hyperuricemia, hyponatremia, hypomagnesemia, and zinc deficiency, are also mentioned among the biochemical abnormalities that may occur during the use of the KD, but they are easily correctable (Kang et al., 2004; Kossoff et al., 2009a, Cervenka, Kossoff, 2013). The impact of the KD on haematological parameters was assessed in a group of 33 children with refractory epilepsy. A statistically significant increase was found after 6 and 12 months in the haemoglobin, haematocrit, MCV and after 12 months in Vit B12 (Kose et al., 2018).

Although the KD can cause a number of adverse effects, they are not the main reason for interrupting the therapy. Usually, the treatment is discontinued due to a lack of satisfactory efficacy (49.9%), or difficulty in adapting to its restrictions (11%). Adverse effects are mostly mild and easy to manage or can be prevented. The occurrence of more serious, potentially fatal complications, is not more frequent than during the natural course of symptomatic epilepsy in children. Further studies are needed to assess the long-term effect of the KD on health, even many years after the end of the treatment. The potential link between hyperlipidaemia, even transient, and the development of atherosclerosis and cardiovascular diseases later in life should be examined in particular (Cai et al., 2017).

Cost effectiveness of the KD
Several recently published studies have attempted to assess the economic aspect of the KD in the treatment of refractory epilepsy in comparison to pharmacological treatment (care as usual – CAU) and the VNS. The cost differences between KD and CAU were not considered. The VNS, compared to standard treatment and KD, was more expensive over a 12-month period, while over 5 years it was definitely more economically advantageous (de Kinderen et al., 2011; de Kinderen et al., 2015; de Kinderen et al., 2016; Wijnen et al., 2017). In addition, the number of hospital admissions and visits to the hospital emergency department was analysed in a group of 37 children with refractory epilepsy. A 12-month period of treatment with the KD was compared to the 12 months prior to its intro-
duction. The number of visits to the emergency unit decreased by 36%, and there were also 40% fewer hospitalisations with a 39% reduction in hospital days. As a result, there was a decrease in the cost associated with hospital treatment and emergency department interventions in the group of children treated with the KD (Kayyali et al., 2016). This issue also requires further long-term research on larger groups of patients taking into account the direct and indirect costs of each form of therapy used.

CONCLUSIONS AND FUTURE PROSPECTS

1. The KD is currently a well-established therapy for refractory epilepsy in children. Its efficacy has been confirmed not only by clinical observations in groups of patients or individual cases, but also by randomised trials.
2. There has been an increasing number of reports on the successful use of the KD in adult patients, especially its more liberal versions such as the MAD or the LGIT.
3. The KD is particularly effective in some forms of epilepsies, and should be considered at an early stage of treatment (MAE, Dravet syndrome, West syndrome, FIRES); and diseases in which it is the treatment of choice (GLUT1 DS, PDHD).
4. The KD has also found application in the treatment of urgent conditions such as SRSE.
5. Extensive experience in the KD therapy allows to avoid or successfully treat potential adverse effects, which results in greater efficacy and safety of the treatment.
6. The KD should always be considered, after excluding contraindications, as a therapeutic option in patients diagnosed with refractory epilepsy, regardless of their age. It should not be perceived as a treatment of last resort.
7. Due to the rapidly growing number of children treated with the KD, ‘adult’ neurologists should offer this therapy to their patients as well.
8. Further research on the mechanism of action of the KD, its effectiveness in particular epilepsy syndromes, and potential long-term adverse effects is needed.
9. Possible simplification of the use of the KD, which might lead to its wider application, is also worth investigating.

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