Historical overview

The idea that inclusion or abstinence from certain foods could have benefits for those with seizures has origins that far precede our current era of scientific research. A dietary approach to the treatment of epilepsy can be traced back to the 5th century BC, when Hippocrates described a man whose seizures were cured by abstaining from all food and drink. Guelpa and Marie (1911) are accredited with writing the first scientific account of the benefits of fasting in epilepsy. In 1921 Geyelin also reported the successful use of fasting, with 20 of 26 fasted patients showing improved seizure control, two remaining seizure-free for over a year. The arbitrary length of fasting was 20 days, although only four had seizures after the tenth day without food (Geyelin, 1921). Geyelin was inspired by the work of Conklin, an osteopath who believed that epilepsy was caused by the release of a toxin from the Peyer’s patches of the intestine which was taken up by the lymphatic system and periodically released into the blood, triggering seizures. Conklin therefore advocated complete gut rest and starved his patients for up to 25 days. He reported a 90% success rate in children under the age of 10 years, decreasing to 50% in those aged 25–40 years; success was more limited in the older adults (Conklin, 1922). These observations sparked considerable clinical and research interest, and linked with ongoing studies examining ketoacidosis and the disturbance in glucose metabolism that occurs in diabetes.

During starvation, the body passes through various phases of metabolic adaptation to spare muscle protein breakdown and draw on the energy reserves of body fat. Skeletal muscle and other tissues progressively switch energy source from glucose to free fatty acids generated from triglyceride breakdown. There is increased oxidation of fatty acids in the liver, with increased production of the water-soluble ketone bodies acetoacetate and β-hydroxybutyrate. Ketone bodies
can be used as an alternative fuel by many tissues, most notably the brain, as unlike fatty acids they are able to pass across the blood–brain barrier. Blood ketone-body levels will continue to increase during the first 3 weeks of starvation during which the brain adapts to them as its primary energy source. (See Chapter 5 for further detail on biochemical changes and their connection with our current understanding of how dietary treatments may work.)

Prolonged starvation as a means to treat epilepsy had obvious practical limitations, and it was first suggested by Wilder (1921a) that a diet very high in fat and low in carbohydrate might mimic the benefits of fasting by causing a similar ketotic effect. He tried this proposed ‘ketogenic diet’ (KD) on three of his patients at the Mayo Clinic and reported significant seizure control (Wilder, 1921b). Peterman, a fellow worker at the clinic, reported further successful results in children treated with this KD (Peterman, 1924). Talbot and his co-workers introduced the idea of a preliminary fast before commencing the diet, with a gradual build-up of dietary fat over the following few days. His clear instructions on how to calculate the diet form the basis of the classical KD calculations used widely today (Talbot et al., 1927; Talbot, 1930; see Chapter 8).

Other early studies also reported the wide use and success of the KD (Helmholz, 1927; McQuarrie and Keith, 1927; Lennox, 1928; Wilkins, 1937). The discovery of new anticonvulsant drugs at the end of the 1930s distracted clinical and research interest from diet and towards medications, the latter perceived to be both simpler and more palatable to use. Increasing realization that not all seizures respond to drugs and concerns about medication side effects and the possible ramifications of prolonged intractable seizures, especially in the context of childhood development, have renewed interest in dietary treatments. The past few decades have seen a steady proliferation of published research, accompanied by a broadening of clinical application extending beyond the traditional classical form of KD. While this is still used extensively today, alternative types of KD therapy have allowed a more flexible approach to dietary treatments for epilepsy.

The classical and medium-chain triglyceride KD

Early studies in children by Wilder, Peterman and Talbot used a diet of 1 g protein per kilogram body weight, with 10–15 g carbohydrate daily, the remaining energy supply being from fat. Fat was primarily animal based, in the form of butter, lard and cream. The term ‘ketogenic ratio’ was used to describe the ratio of ketone-producing foods in the diet (fat) to foods that reduced ketone production (carbohydrate and protein). Seizure control was found to be optimal with a ratio of 3 or more. This led to the terminology of a 3 : 1 KD (87 % of total dietary energy derived from fat) or 4 : 1 KD (90 % of total dietary energy derived from fat). This is the basis of the classical KD used today. Carbohydrate intake is very limited: bread, cereals, pasta or rice are generally not allowed, the main carbohydrate sources being controlled portions of vegetables or fruit at each meal. Protein is
kept to a minimum to meet requirements: a source can be included at each meal, such as meat, fish, egg or cheese, but protein foods that contain additional sources of carbohydrate are generally avoided. The macronutrient composition of this type of diet is substantially different from an average UK diet (Figure 1.1).

A modification of the classical KD was proposed in 1971, using medium-chain triglyceride (MCT) as an alternative fat source (Huttenlocher et al., 1971). The main constituents of MCT are the medium-chain octanoic and decanoic fatty acids, which are absorbed more efficiently than their long-chain counterparts, and which are carried to the liver in portal blood bound to albumin. This is in contrast to long-chain fatty acids, which are incorporated into chylomicrons and transported via the thoracic duct through the lymph system, exiting into the circulation at the left subclavian vein from where they are carried via peripheral

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**Figure 1.1** The composition of ketogenic diet treatments: approximate percentages of dietary energy from fat, protein and carbohydrate. (a) Recommended UK diet; (b) classical 4:1 ratio ketogenic diet; (c) MCT ketogenic diet; (d) modified Atkins diet (at 1:1 ketogenic ratio); (e) low glycaemic index treatment.
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tissues to the liver. After hepatic tissue uptake, medium-chain fatty acids can pass directly into liver mitochondria for subsequent oxidation and ketone body synthesis. Long-chain fatty acids require carnitine for their transport across this mitochondrial membrane. These differences in MCT metabolism facilitate a more rapid and greater oxidation of medium-chain fatty acids, resulting in a higher ketone yield per kilocalorie of dietary energy than that from long-chain fat. Therefore less total fat is needed in the diet to achieve the desired level of ketosis. More protein and carbohydrate can be allowed with the aim of improving palatability and patient acceptance.

Huttenlocher went on to show that a KD providing 60% of total dietary energy from MCT was as effective as a 3:1 classical diet in producing ketosis and controlling seizures in 12 children with epilepsy (Huttenlocher, 1976). This amount of ingested MCT, particularly if introduced too quickly, can cause gastrointestinal side effects, primarily diarrhoea and abdominal discomfort. Although these can be ameliorated with dietary adjustment, in some individuals a more moderate prescription may be appropriate. Schwartz and her colleagues suggested a modified MCT diet, providing 30% of dietary energy from MCT and an extra 30% from long-chain fats such as butter or cream; this has been termed the John Radcliffe diet. They also reported no difference between the classical, MCT and modified MCT KDs in controlling seizures in a non-randomized study (Schwartz et al., 1989). A more recent randomized trial by our group also showed neither the classical nor MCT KD to be superior when assessing efficacy or tolerability after 3, 6 or 12 months of treatment (Neal et al., 2009). Further details on the classical and MCT KD can be found in Chapters 8 and 9.

Alternative KD therapies

In the last decade two other types of KD therapy have been used with success. The modified Atkins diet (MAD) was first used in 2002 for two children at the Johns Hopkins Hospital in Baltimore, USA. One child was waiting for a scheduled admission to start the classical KD; another had discontinued classical KD a year before. Seizures were successfully controlled with the MAD in both cases (Kossoff et al., 2003). This diet restricts carbohydrates, encourages high-fat foods, but does not limit or measure protein or total calories. The principles are based on the popular weight loss diet first described by Dr Robert C. Atkins in 1972 (Atkins, 1972), with the primary outcome goal of weight loss replaced by one of seizure control. Carbohydrate is usually restricted to 10–20 g per day and review of dietary records shows that the approximate ratio of fat to carbohydrate and protein is 1:1 compared with 3:1 or 4:1 with the classical KD. There is a growing body of scientific publications reporting successful use of the MAD.

An alternative diet, the low glycaemic index treatment (LGIT), was first described in 2005 (Pfeifer and Thiele, 2005). This diet restricts carbohydrates to 40–60 g per day but only allows those with a glycaemic index of less than 50, the
aim being to minimize increases in blood glucose. Food is not weighed but based on portion sizes. Protein, fat and calorie intake is loosely monitored, albeit considerably less strictly than on traditional KDs. Unlike the MAD, a high-fat intake is not actively encouraged.

Figure 1.1 illustrates the differences in dietary composition of these alternative dietary treatments as compared with traditional KDs. Because of the flexible nature of the MAD and LGIT, the percentages of energy from the different macronutrients may vary between individual diets; the figures chosen give the reader some idea of how an average diet might look. Further details on the MAD and LGIT can be found in Chapters 10 and 11.

Other non-KD treatments

There have been suggestions that food intolerance could be linked to epilepsy in the literature, although these are mostly anecdotal and uncontrolled reports. A 1968 review of 26 studies examining a relationship between epilepsy and allergies concluded that pollen, dust and moulds were the main culprits (Fein and Kamin, 1968). In a study examining the role of oligoantigenic diets in 63 children with epilepsy, 45 of whom had associated headaches, abdominal symptoms or hyperkinetic behaviour, 37 had improved seizures on an elimination diet (Egger et al., 1989). However, the 18 children with epilepsy alone showed no improvement. A further study of the same elimination diet failed to demonstrate any benefit in nine children with epilepsy (Van Someren et al., 1990). Although it is possible that allergic reactions could trigger seizures in susceptible patients, the present evidence does not support the use of elimination diets in epilepsy treatment and further detail on this type of dietary therapy is not included in this book.

Application and availability of KD therapy

The classical and MCT KDs are primarily used in children, although studies have demonstrated benefit in infants (Nordli et al., 2001; Hong et al., 2010), adolescents (Mady et al., 2003) and adults (Sirven et al., 1999); the MAD has also been demonstrated effective in treating adults (Kossoff et al., 2008a). The flexible protocols employed in both the MAD and LGIT are clearly useful for adolescents and adults with epilepsy who may prefer a less rigid dietary treatment, but they can also be used with success as an alternative for children. Although most of this book will refer to children, a separate chapter on adults is also included. As well as being successfully used to treat epilepsy in all age groups, the KD is an important treatment for two metabolic disorders, glucose transporter (GLUT)-1 deficiency and pyruvate dehydrogenase deficiency (see Chapter 27).

Worldwide use of the KD has increased dramatically since the early 1990s. Although the greatest number of centres offering this treatment are in the USA,
a survey reported KD programmes in 41 other countries, 16 of which had multiple centres (Kossoff and McGrogan, 2005). Most geographic regions were represented, with the exception of the majority of Africa and Central America. Most of the larger centres in the USA used a classical KD protocol at the time of this survey, but European and worldwide KD practice was more varied, with both classical and MCT diets being employed. Both protocols are used within the UK; a postal survey of 280 British Dietetic Association Paediatric Group members in 2000 found 22 centres were using the KD, 13 the classical and nine the MCT (Magrath et al., 2000). The survey was repeated in 2007 and although use of the KD had risen by 50%, numbers were still small as this only represented an increase of 51 patients (Lord and Magrath, 2010). At the time of this survey, no dietitians reported using MAD or LGIT. Similar to reports from other European centres (Kossoff and McGrogan, 2005), a lack of funding resources and dietetic time was identified as the main barrier to greater use of dietary treatments. Since these studies were published, practice has changed considerably, with many more centres in the UK and around the world now using the MAD, and a smaller but growing number the LGIT. Using MAD as a dietary treatment for epilepsy in developing countries is also being explored (Kossoff et al., 2008b). Neurologists are becoming more aware of dietary therapies, but many continue to reserve its use until a child has failed a number of anticonvulsants.

The successful use of more relaxed KD therapies is leading the way towards a flexible, rather than rigid, approach to dietary treatment of epilepsy; this may include components of the various protocols drawn together to provide a treatment individually tailored to specific dietary and lifestyle requirements. A clear understanding of how the different types of diet are calculated and implemented is essential before they can be adapted in such a way and this book aims to provide the information to help foster this understanding. The inclusion of guidance on when to use KD therapy, how to initiate, calculate, fine-tune, monitor and discontinue treatments, the potential side effects, use in infants and adults as well as children, and practical advice from both parent and dietitian, will provide readers with a comprehensive and practical training on all aspects of implementation.

References


