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VIEWPOINT

Ketogenic diet for epilepsy and obesity: Is it the same?

A. Tagliabue [a], M. Armeno [b], K.A. Berk [c], M. Guglielmetti [a,*], C. Ferraris [a], J. Olieman [c], E. van der Louw [c]

[a] Ketogenic Metabolic Therapy Laboratory, Department of Public Health Experimental and Forensic Medicine, University of Pavia, Italy
[b] Ketogenic Diet Team Unit, Clinical Nutrition Department, Hospital Pediatría Prof Dr JP Garrahan, Buenos Aires, Argentina
[c] Department of Internal Medicine, Division of Dietetics, Erasmus MC University Medical Centre Rotterdam, Rotterdam, the Netherlands

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Abstract The term "ketogenic diet" (KD) is used for a wide variety of diets with diverse indications ranging from obesity to neurological diseases, as if it was the same diet. This terminology is confusing for patients and the medical and scientific community. The term "ketogenic" diet implies a dietary regimen characterized by increased levels of circulating ketone bodies that should be measured in blood (beta-hydroxybutyrate), urine (acetoacetate) or breath (acetone) to verify the "ketogenic metabolic condition". Our viewpoint highlights that KDs used for epilepsy and obesity are not the same; the protocols aimed at weight loss characterized by low-fat, low-CHO and moderate/high protein content are not ketogenic by themselves but may become mildly ketogenic when high calorie restriction is applied. In contrast, there are standardized protocols for neurological diseases treatment for which ketosis has been established to be part of the mechanism of action. Therefore, in our opinion, the term ketogenic dietary therapy (KDT) should be reserved to the protocols considered for epilepsy and other neurological diseases, as suggested by the International Study Group in 2018. We propose to adjust the abbreviations in VLCHKD for Very Low CarboHydrate Ketogenic Diet and VLEKD for Very Low Energy Ketogenic Diet, to clarify the differences in dietary composition. We recommend that investigators describe the researchers describing efficacy or side effects of KDs, to clearly specify the dietary protocol used with its unique acronym and level of ketosis, when ketosis is considered as a component of the diet's mechanism of action.

1. Introduction

The term "ketogenic diet" (KD) is used for a wide variety of dietary forms with diverse indications ranging from obesity to neurological diseases, as if it was the same diet. The term is sometimes used even for diets that do not induce ketosis at all, which is odd from a linguistic point of view. In fact, "ketogenic" means production and maintenance of circulating ketone bodies.

Moreover, the term would imply that "ketosis" is part of the mechanism of action of the dietary therapy itself. While this holds true for epilepsy [1] and GLUT1-DS [2], where ketones are an alternative nourishment for the brain, the role of ketosis in obesity treatment is unclear and limited to a controversial reduction in hunger [3].

However, the types of diets that induce a measurable level of ketosis are few and well characterized. This

* Corresponding author.
E-mail address: monica.guglielmetti@unipv.it (M. Guglielmetti).

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overview aims to provide more clarity regarding the different forms of ketosis-inducing diets and their terminology.

2. Ketogenic diet nomenclature confusion

The first consensus statement of the International Study Group on Ketogenic Diet for epilepsy [4] appoints "ketogenic diet" as a non-pharmacologic treatment used worldwide to treat children with intractable epilepsy since 1921. It consists of a high-fat low–carbohydrate (CHOs) diet, based on ratios (grams fats/grams proteins + CHOs), with adequate caloric content to ensure adequate growth. In the updated recommendations [5] the term "ketogenic diet" has been substituted by "ketogenic dietary therapies" to underline the existence of different standardized protocols, with different ratios, to be used to treat epilepsy and other neurological diseases. It requires strict monitoring of ketone levels. In both reports, weight loss is considered among the side effects to be avoided by ensuring an adequate calorie intake of high fat foods. Recently, we have reported that a full calorie classic ketogenic diet is adequate to support growth in children [6] even in the long-term follow-up.

On the contrary, in the obesity and endocrine-metabolic diseases field, "ketogenic diets" are intended for weight loss purposes [7] and induce ketosis mainly by calorie restriction. Many trials have compared the impact of different diet compositions on weight loss, one example being the study by Yancy et al. (2004) [8] in which a "low-CHO, ketogenic diet" is tested versus a low-fat diet". The "ketogenic" regimen used by Yancy et al. is intended as an Atkins-like diet with a very-low CHO content (<20 g) in the initial phase, which is increased during subsequent periods, and an unrestricted amount of foods high in protein/fat (e.g. dairy, meat, fish). In the field of obesity, low CHO diets can be moderate or high in fat and moderate or high in proteins and do not necessarily result in ketosis [9]. At a given amount of CHOs the protein quantity appears to influence ketogenesis, as some amino acids are used for gluconeogenesis. *Yancy* et al. (2004) [8] reported only trace levels of urinary ketones in 86 % of their patients after two weeks of diet, with ketone levels decreasing thereafter. This dietary approach is referred to as *Very Low Carbohydrate Ketogenic Diet* (*VLCKD*) by several authors [10,11]. Unfortunately, the same acronym *VLCKD* is also used for *Very Low Calorie Ketogenic Diet*, a dietary therapy which induces ketosis through semi-starvation and is indicated for severe obesity [12].

Recently, a few authors have addressed this confusion in the terminology for ketogenic dietary therapies. In 2018, Bistrian [11], in a letter to the Editor of Pediatrics, described his opinion on the existence of two types of ketogenic diet: "*One type of ketogenic diet is the very low–calorie diet, or semistarvation ketogenic diet, which is severely hypocaloric and provides* 800 kcal *per day (and usually* 400 kcal *per day), and is intended for the weight loss phase in the medical treatment of obesity ….a second type of ketogenic diet, called a eucaloric ketogenic diet, is also used to restrict carbohydrate intake to a similar degree but contains substantially more total calories because fat is intended to provide sufficient energy to allow growth in children while helping to establish seizure control …*"

In 2020 Trimboli et al. [13] published a paper named "Confusion in the nomenclature of ketogenic diets blurs evidence" to point out that several publications have analyzed the clinical effects of ketogenic diets as if they were alike. They proposed a definition based on the CHO content: "*For a diet to be defined as ketogenic, the only requirement is represented by the carbohydrate restriction, usually to less than 30–50 g/day*" and distinguish three types of ketogenic diet: very low-calorie, low-calorie and eucaloric ketogenic diets.

Recently, we commented on the paper by Moriconi et al. [14], stating that the interpretation of the available results on *Very Low Calorie Ketogenic Die*t from the literature is currently hampered by differences in diet composition, and incomplete reporting on diet composition and ketone levels. We concluded that consensus on these issues in the field of obesity-related T2DM is necessary in order to improve the quality of study designs, interpretation and reproducibility of data.

In 2021, Volek et al. [15] state that "*ketogenic diets are a subset of low-CHOs diets that usually consist of less than 50 g of CHOs per day with adequate but not excessive protein, and varying amounts of fat depending on the intended body weight goals. Energy content can fluctuate from very low-calorie (*e.g., *semi-starvation,* < 800 kcal*/day) to mildly hypocaloric to eucaloric diets*".

Notwithstanding these tentative approaches to clarify, no consensus has been reached to an unambiguous definition of the KD. It is important to underline that the restriction of CHOs is not sufficient to define a diet as ketogenic, as proposed by Trimboli (2020) [13] and Volek (2021) [15] but the calories and the ratio between ketogenic and anti-ketogenic nutrients needs to be taken into consideration, as described in the following paragraphs [16].

3. What is really a ketogenic diet?

Nowadays several diets are referred to as ketogenic such as: Classic Ketogenic Diet (CKD), MCT Ketogenic Diet (MCT-KD), Modified Atkins Diet (MAD), Very Low-Carbohydrates Ketogenic Diet and Very Low-Calorie Ketogenic Diet, both referred as VLCKD. A detailed description of each dietary protocol in chronological order is reported as Supplementary Material (**S1**).

Fig. 1 compares the relative macronutrient composition of different ketogenic diets according to their caloric content. Energy prescription is tailored on the individual's requirements in CKD, MCT-KD e MAD protocols. Therefore, these are generally eucaloric dietary regimens, ranging from 500 kcal/day (in infants) to 2500 kcal/day or above (in normal-weight adults). Very Low Carbohydrate

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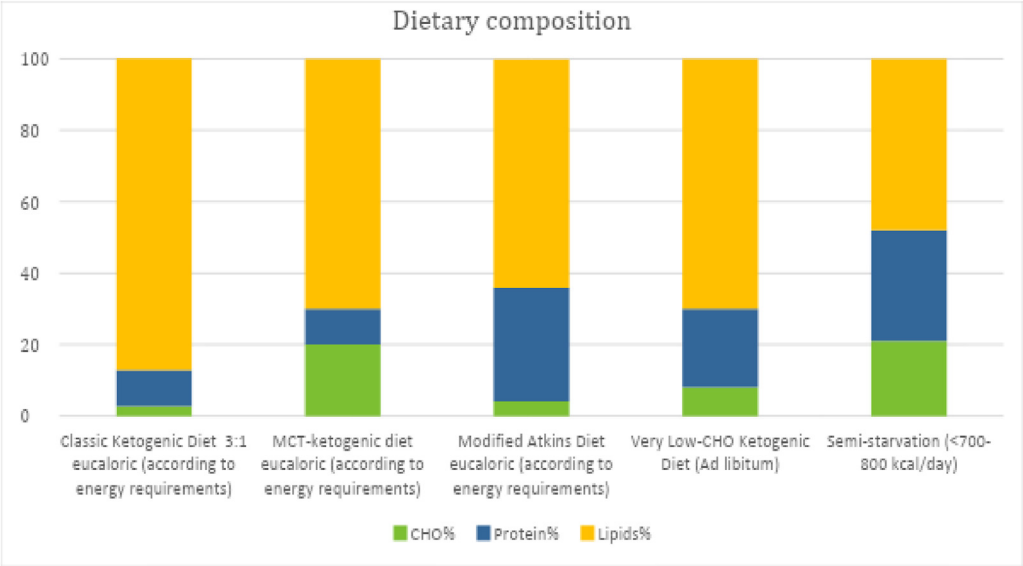

Figure 1 Relative macronutrient composition of different ketogenic diets.

Ketogenic diets are characterized by ad libitum calorie intake but usually result in a reduced energy intake due to various mechanisms [9,17]. Very Low-Calorie Ketogenic Diets are strictly hypo-caloric *per* definition, reaching a maximum of 700–800 kcal/day [18].

The term "ketogenic" diet implies a dietary regimen characterized by increased levels of circulating ketone bodies that should be measured in blood (beta-hydroxybutyrate), urine (acetoacetate) or breath (acetone) to verify the "ketogenic metabolic condition" [19]. In fact, KD mimics the metabolic effect of fasting during an anabolic state [1,20].

A first problem arises because most published papers on "KD" do not specify the level of ketosis intended to achieve in order to obtain the therapeutic effect and most of them do not even report achieved ketone levels. Since ketosis is assumed to be part of the therapeutic action, it makes no sense to speak of a KD without specifying the degree of serum ketones elevation that the diet is intended to achieve, as underlined by Theodore Van Itallie, obesity expert and leading researcher in metabolic diseases [21].

Unfortunately, no agreement has been reached on the ketosis level target in different medicine fields in which KDs are currently investigated. One exception is GLUT 1-Deficiency Syndrome (GLUT1-DS) which is nowadays treated with a eucaloric KD. To provide ketones for brain nourishment in GLUT1-DS, blood beta-hydroxybutyrate level should be maintained in the 4–5 mmol/L range [2]. In epilepsy, a range between 2 and 4 mmol/L is suggested to correlate with seizure reduction [19]. In our experience these levels can be reached and maintained for several years, if careful medical monitoring is applied [22] These ketone levels can be reached in the CKD and MCT-KD protocols [23].

In studies on obesity, no target values of ketosis are suggested or discussed even if ketosis is considered relevant to hunger suppression [3]. Recent studies using Very Low-Calorie Ketogenic Diets report levels of mild ketosis (i.e. beta-hydroxybutyrate in the range 0.5–1.2 mmol/L) in the active ketosis phase [24,25]. In sports medicine keto-adaptation has been defined as a change from 0.1 to 0.5 mmol/L of beta hydroxybutyrate [26] while Volek et al. (2021) [15] define nutritional ketosis starting at a blood level of beta-hydroxybutyrate (the predominant circulating 'ketone') of 0.5 mmol/L and extending up to 5 mmol/L. All the above-mentioned ketone levels are well below ketoacidosis, which occurs when blood ketones enter a range of 10–25 mmol/L [27].

As clearly illustrated in Table 1 we may distinguish hyper-ketonemic diets with indications for neurological diseases and mildly ketogenic diets popular for weight loss purposes, as firstly underlined by Van Itallie in 2003 [21]. In this table, we presented the main characteristics of the different ketogenic dietary approaches, in terms of: (1) macronutrients and energy intake, (2) reported blood ketone levels and (3) prevailing use. The diet description was based on the most recent consensus/recommendations for each dietary protocol. Reported β-hydroxybutyrate levels were extrapolated by the experimental studies or reviews that evaluated ketonemia levels. Prevailing use was described on the basis of consensus, reviews and/or the original articles that first proposed them for the specific disease.

The level of ketosis induced by a specific diet is determined by its ketogenic potential as explained in the following paragraph.

4. Ketogenic potential

The characteristics of the diet that influence the level of ketone production is commonly referred to as "ketogenic potential" [5,28,29], and depends on the composition of

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Table 1 Different ketogenic dietary approaches in epilepsy/neurological diseases and obesity treatment.

Diet description (abbreviation)	Carbohydrates	Lipids	Protein	Energy	*Reported Blood Ketone Levels (β-hydroxybutyrate)*	Prevailing use according to literature (ref)
Classical Ketogenic Diet (CKD) [2,5,23]	3–15 % energy	70–90 % energy	According to Dietary Reference Values for age range	According to energy requirements	>1.5 and up to 5 mmol/L in children [28,45,46]	Seizure control, brain energy substrate i.e. epilepsy, GLUT1-DS and other neurological diseases [2,5,23]
Medium Chain Triglycerides Ketogenic Diet (MCT-KD) [5]	20 % energy	10–25 % (infants) 40–60 % (adults)	According to Dietary Reference Values for age range	According to energy requirements	>1.5 and up to 5 mmol/L in children [28,45,46]	Seizure control, brain energy substrate i.e. epilepsy and other neurological diseases [2,5,23,47]
Modified Atkins Diet (MAD) [5]	10 g in children 15 g/day in adolescents 20 g/day in adults	Not measured, fat sources are encouraged	Ad libitum	According to energy requirements; caloric intake needs to be verified during the treatment	Variable depending on food choices and caloric intake	Seizure control, brain energy substrate i.e.epilepsy and other neurological diseases [5,48]
Very Low-Carbohydrate Ketogenic Diet [9]	<20–50 g/day	Not specified	Not specified	Ad libitum	0.5–1.5 mmol/L Ketosis may not occur depending on individual variability [49,50]	Weight loss, glycemic control i.e.obesity diabetes and other endocrine-metabolic diseases [10,51]
Very Low-Calorie Ketogenic Diet *Semi-starvation* [18]	<30–50 g/day	<30–40 g/day	0.8–1.2 g/kg ideal body weight	<700–800 kcal/day	0.5–1.2 mmol/L in the active ketosis phase [24,25]	Weight loss, glycemic control i.e.obesity diabetes and other endocrine-metabolic diseases, migraine [18,52]

GLUT1-DS = GLUT1 Deficiency Syndrome.

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oxidized nutrients which can be derived from the diet or from endogenous deposits (i.e. adipose tissue).

An increased production of ketone bodies by the liver is the consequence of insufficient glucose availability which determines a metabolic shift towards an increased fatty acid oxidation. The excess Acetyl CoA that cannot be used in the Krebs cycle leads to increased production of ketones.

In physiological conditions, insufficient glucose availability may be derived from two conditions: CHO restriction during a eucaloric diet or severe caloric restriction (prolonged fasting).

The first condition is the substitution of CHOs with fat-rich-foods during a eucaloric diet and maintaining an adequate/low protein intake. In this situation, the shift in metabolism is due to increased exogenous fat oxidation and results in ketosis without weight loss. More specifically, the ketogenic potential of a eucaloric diet depends on the ratio between ketogenic and non − ketogenic dietary substrates, named *ketogenic ratio,* and described by Woodyatt (1921) [30]. This author experimentally determined values for the ketogenic and anti-ketogenic properties of dietary components and developed the following formula for the *dietary ketogenic ratio calculation:*

$$\frac{0.9\,\mathrm{L\,(g)} + 0.46\,\mathrm{P\,(g)}}{\mathrm{C\,(g)} + 0.1\,\mathrm{L\,(g)} + 0.58\,\mathrm{P\,(g)}}$$

where L represents dietary lipids in grams; P represents dietary protein in grams; C represents dietary CHO in grams. The presence of protein in both the numerator and denominator of this formula is attributed to the different metabolic pathways used for specific amino acids that comprise dietary protein (mainly gluconeogenesis, to a lesser extent ketogenesis, or both). Since most amino acids are glucogenic, the formula has been simplified for clinical practice, including protein content only in the denominator as follows:

$$\mathrm{L\,(g)} \;/\; (\mathrm{C\,(g)} + \mathrm{P\,(g)})$$

The ratio at which significant ketosis first appears has been called the threshold of ketogenesis by Wilder (1922) [31], who experimentally determined such a threshold as 2:1 (2 g of fat opposite 1 g of protein plus CHOs). In current clinical practice, dietary ketogenic ratios in the range of 1:1 to 4:1 are used in treating epileptic patients depending on the age of the patient and on the target value of ketosis to be achieved [5]. Even with the highest dietary ratio (4:1) the levels of circulating ketones do not reach the dangerous levels of diabetes ketoacidosis, and pH values remain in the normal range [29].

In 2018, Zilberter and Zilberter [16] reviewed 62 studies that reported on CHO-restricted dietary interventions described as “ketogenic” and found that only 25 out of 62 had a ratio of >1.5:1. Again, this illustrates the complexity of interpreting the available evidence on KDs, since the majority of the studies described diets that were not ketogenic in terms of ratio.

The second condition is prolonged fasting or severe caloric restriction. In these situations, the body derives energy from endogenous fat oxidation resulting in ketosis and weight loss.

The Woodyatt formula works only for a eucaloric diet since it fails to consider the utilization of energy stores in a hypocaloric diet. In a hypocaloric regimen, endogenous fat is oxidized in greater quantities with greater energy deficit. The amount of endogenous fat may be estimated based on the energy deficit and the composition of the weight loss (75 % fat and 25 % FFM) and included in the calculation of the ketogenic potential [32].

Cohen IA (2009) [33] modified the ketogenic ratio equation, considering the amount of endogenous fat oxidized, to express the *total ketogenic ratio* as follows:

$$\frac{0.9\,\mathbf{TL}\,\mathrm{(g)} + 0.46\,\mathrm{P\,(g)}}{\mathrm{C\,(g)} + 0.1\,\mathrm{L\,(g)} + 0.58\,\mathrm{P\,(g)}}$$

where TL (Total Lipids) represents the sum of dietary and endogenous fat in grams; P represents dietary protein in grams; C represents dietary CHO in grams. This equation can be simplified as:

$$\mathrm{TL\,(g)} \;/\; \mathrm{C\,(g)} + \mathrm{P\,(g)}$$

Summarized, the ketogenic potential of a eucaloric diet depends on the restriction of CHOs but only if the amount of protein does not exceed the physiological needs whereas the ketogenic potential of a hypocaloric diet depends on the energy deficit: the higher the energy deficit, the higher the ketogenic potential.

Table 2 illustrates examples of ketogenic ratio calculations for the different KD protocols previously described. The dietary ketogenic ratio includes dietary fat while the total ketogenic ratio includes both dietary fat and endogenous fat which is used under hypocaloric conditions. The values are based on the assumption that the energy restriction required for 1 kg of weight loss amounts to 7000 calories/week (i.e. 1000 calories *per* day) and the weight loss is 75 % fat [32]. From this, we can calculate the weight loss from daily caloric restriction and fat loss as 75 % of weight loss; the grams of oxidized fat (endogenous lipids) are added to dietary lipids (exogenous lipids) to obtain total lipids to be used in the calculation of the total ketogenic ratio.

For the KDs used in neurological disorders treatment, we presented the calculations both for eucaloric (first line) and slightly hypocaloric diets (500 kcal of deficit; second line), prescribed for a reference person with a daily energy requirement of 2000 kcal. In fact, in cases of overweight and obese epileptic/neurological patients it my be appropriate to apply a slight-moderate calorie restriction to achieve a modest weight loss (2 kg in a month). These approximate calculations are useful to highlight the increase of the ketogenic ratio (and therefore ketogenic potential) when reducing the calorie intake even when using the same ketogenic protocols. CKD, MCT-KD and MAD are not aimed at weight loss, but in specific individuals, a moderately hypo-caloric version of these protocols can be prescribed.

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Table 2 Examples of calculation of ketogenic ratios of eucaloric and hypocaloric diets for an adult individual with energy requirement of 2000 kcal/day.

Diet description (abbreviation)	Calories	Caloric restriction	CHOs	Protein	Exogenous lipids	Endogenous lipids	Total lipids	Dietary ketogenic ratio	Total ketogenic ratio
CKD 3:1	2000 kcal/day	NA	14 g/day	50 g/day	194 g/day	NA	194 g/day	3:1	3:1
CKD 3:1	1500 kcal/day	500 kcal/day	8 g/day	40 g/day	145 g/day	42 g/day	187 g/day	3:1	3.9:1
MCT-KD	2000 kcal/day	NA	100 g/day	50 g/day	155 g/day	NA	155 g/day	1:1	1:1
MCT-KD	1500 kcal/day	500 kcal/day	75 g/day	38 g/day	117 g/day	42 g/day	159 g/day	1:1	1.4:1
MAD	2000 kcal/day	NA	20 g/day	160 g/day	142 g/day	NA	142 g/day	0.8:1	0.8:1
MAD	1500 kcal/day	500 kcal/day	20 g/day	115 g/day	107 g/day	42 g/day	149 g/day	0.8:1	1.1:1
Very Low-CHO KD	1250 kcal/day	750 kcal/day	24 g/day	70 g/day	97 g g/day (70 %)	63 g/day	160 g/day	1:1	1.7:1
Semi-starvation	750 kcal/day	1250 kcal/day	40 g/day	58 g/day	40 g/day	104 g/day	144 g/day	0.3:1	1.1:1

CHOs = carbohydrates; CKD=Classical Ketogenic Diet; MCT-KD = Medium Chain Triglycerides Ketogenic Diet; MAD = Modified Atkins Diet; VLCKD=Very Low-Carbohydrate Ketogenic Diet.

5. Commercial products used in ketogenic dietary protocols

The same confusion of terminology which we have described for dietary protocols exists also for the commercial products. To date, several food products, commercialized as “ketogenic”, are available and the market continues to expand. Among them, it is important to highlight the difference between high-fat ketogenic ones developed specifically for the treatment of neurological diseases and those which are intended for weight loss. Generally, these are high-protein and low-CHOs products, with a small fat component. Ketogenic high fat products include powder or liquid formulas, formulations enriched with MCTs and/or LCTs, baking mixes and ready-to-eat products (i.e. biscuits, bread, etc.) [34]. Due to their composition, they have a medium−high ketogenic ratio. High-protein and low-CHOs products are mainly developed as alternatives to the commonly used cereal-based products (i.e. pasta). They have a low ketogenic ratio, being fats underrepresented, while proteins are the main component. So, they are inappropriately called “ketogenic”, because they do not have ketogenic potential. This distinction is important both for patients and nutrition specialists in order to prescribe the correct dietary plan.

6. Ketogenic diets and side effects

Like all medical therapies, ketogenic diets have potential adverse effects, which need to be known and monitored. The side effects are very different according to: (i) which ketosis inducing diet is prescribed, (ii) which level of ketosis is achieved; (iii) dietary therapy duration; (iv) the overall quality of the diet and the proportion of plant/animal origin protein and fats.

According to the Committee’s conclusions in the Consensus Statement [5], in epilepsy treatment, the overall risk of serious adverse events is low for all the ketogenic dietary therapies considered (Classic, MCT and MAD). In the short-term, gastrointestinal complaints are the most common but they can be present also during the maintenance phase. In both cases it can be mostly remedied. During long-term KD therapy, several side effects are described such as hyperuricemia, hyperlipidemia, kidney stones, osteopenia and delayed growth in children. Considering the last point, recent studies reported that, if appropriately monitored, KDs are adequate to support growth in children [6] even in the long-term follow-up [35].

The risk of adverse effects occurrence is linked to the KDs composition: lower ratio KDs (i.e. MAD) are associated with fewer side effects [36]. To avoid side effects related to an increased consumption of saturated fatty acids, careful planning of the diet is required and may benefit from the adoption of practical suggestions based on a Mediterranean dietary pattern as we have recently suggested [37]. Observational studies conclude that using plant-based fat and protein sources in low CHO diets is associated with lower mortality, whereas animal-based fat and protein sources are associated with higher mortality [38,39]. However, in epilepsy treatment KDTs do not need to be discontinued for most adverse effects even in young infants [35,40]. In patients with type 1 glucose transporter deficiency, in whom the ketogenic diet is the treatment of choice and is generally followed for many years, adverse effects should be prevented and monitored especially in the long term [41]. Therefore, when indicated, KDT needs to be implemented and monitored by an expert multidisciplinary keto-team.

Medically supervised very-low-calorie diets (<800 kcal/day) have been used for over 40 years for the treatment of severe obesity and their side effects have been clearly described [9]. The recent introduction of a multiple-phase VLCalorieKD protocol with the use of meal replacements limits the “ketogenic phase” to 45 days. The level of ketosis is mild and the duration is very limited therefore also side effects are reduced compared to previous protocols [12] with careful medical monitoring. The most common adverse effects occurring during the initial period are dehydration (due to the natriuretic effect of the low-carbohydrate/low-insulin diet), transient hypoglycemia (which is often mild and asymptomatic), nausea/vomiting, diarrhea, and constipation and halitosis [18].

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Table 3 Adverse effects of ketogenic therapies according to kind of diet and time period.

Type of diet	Adverse effects (AEs)[a]	
KDTs for neurological disorders	*Initiation/short term*	*Maintenance/Longer term*
CDK, MCT-KD, MAD[b] [5]	Common: mild and transient gastrointestinal symptoms (nausea, food refusal, GE reflux) Other (less frequent): dehydration, hypoglycemia, hyperketosis, metabolic acidosis	Common: transient dyslipidemia, constipation and/or diarrhea, hyperuricemia Other (less frequent): kidney stones, growth failure, abnormal bone metabolism
KDTs for obesity and endocrine-metabolic diseases	*Initiation/short term*	*Maintenance/Longer term*
Very low-calorie ketogenic diet (Semi-starvation) [18]	Common: Dehydration related disorders (dry mouth, headache, dizziness/orthostatic hypotension, lethargy and visual disturbances) transient hypoglycemia, halitosis nausea/vomiting, diarrhea/ constipation, hyperuricemia, lipid profile changes Other (less frequent): hypoproteinemia, hypocalcemia and bone damage, urolithiasis, gallstones, hair loss	Not applicable as these protocols are recommended for a maximum period of 12 weeks
Very low-carbohdrate ketogenic diet[c] [9,17]	Common: gastrointestinal complaints (including constipation, nausea, and abdominal pain), Other (less frequent) lightheadedness, dizziness, fatigue, difficulty exercising, poor sleep, headache, skin rash, muscle cramps, weakness, diarrhea, dehydration, hypoglycemia	Common: vitamin/mineral deficiencies, increased LDL −cholesterol, hyperuricemia,

KDTs = Ketogenic Dietary Therapies; CKD=Classical Ketogenic Diet; MCT-KD = Medium Chain Triglycerides Ketogenic Diet; MAD = Modified Atkins Diet; GE = gastro-esophageus; LDL = Low Density Lipoprotein.

[a] All AEs are preventable with close medical supervision.

[b] Alternative KDTs for neurologial diseases such as MAD are associated with fewer AEs than CKD.

[c] These types of diet are often self-prescribed and/or followed without medical supervision, thus an adequate description and monitoring of AEs is difficult.

As for Very-Low Carbohydrate Ketogenic Diets the main problem is the diffusion of this kind of diet for slimming purposes without medical supervision. Atkins-like regimens are often self-prescribed and have potential safety concerns, including increased LDL-cholesterol levels, hypoglycemia, and vitamin and mineral inadequacies [9,17,42]. According to this consideration the European Association for the study of Diabetes recommends against the use of Very-Low Carbohydrate Ketogenic Diets for weight loss in people with type 2 diabetes [43].

In Table 3 we report a detailed description of side effects of the different KDs.

7. Discussion

The term ketogenic diet is nonspecific because ketosis can be induced by different dietary protocols, each of which with a different ketogenic potential (i.e. capacity to induce and maintain nutritional ketosis). The ketogenic potential is proportional to the ratio of ketogenic and not ketogenic nutrients in the diet. Based on this concept, the protocols aimed at weight loss characterized by low-fat, low-CHO and moderate/high protein content (e.g. VLCKDs) are not ketogenic by themselves, but they may become ketogenic when high calorie restriction is applied (due to endogenous fat oxidation). The therapeutic role of ketosis for obesity and diabetes treatment is not well defined apart from a possible reduction in hunger [3].

In contrast, there are standardized protocols *based on the therapeutic effect of ketosis*, developed for neurological diseases treatment. The first one corresponds to the classic ketogenic diet (= high ketogenic ratio diet), a *eucaloric ketogenic* dietary treatment in which high ketone levels are considered a component of the antiepileptic effect through multiple direct or indirect actions [1]. Other, more liberal ketogenic dietary therapies have been proposed, each one characterized by a specific nutrient composition and ketogenic ratio, side effects and indications [5] with the same anti-seizure potential.

In the clinical applications other than epilepsy, the description of ketogenic diets is less defined, varying from a very low-CHO ad libitum protein regimen to a very-low-energy (semi-starvation) diet. Both protocols are at present abbreviated as VLCKD (meaning either Very Low Carbohydrate Ketogenic Diet or Very Low-Calorie Ketogenic Diet) and induce low levels of ketosis. A definitive clarification of the different protocols and fields of application is surely needed. The term “ketogenic” should not be applied for low-CHO diets that do not determine a ketosis state. Ketonemia or ketonuria levels should always be measured. We recommend researchers to clearly explain and identify the dietary protocol used with its specific acronym and detail the nutritional composition. In our opinion, the term ketogenic dietary therapy (KDT) should be reserved to the protocols considered for epilepsy and other neurological diseases as suggested by the International Study Group (2018) [5] and/or protocols for which ketosis is considered part of the mechanism of action as recently hypothesized for acromegaly [44].

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8. Conclusions

Our viewpoint has demonstrated that the answer to the title question "***Ketogenic diet for epilepsy and obesity: is it the same?***" is no, there are several ketogenic dietary regimens with a different ketogenic potential that are used for obesity/diabetes and epilepsy/neurological disease. Researchers describing efficacy or side effects of ketogenic diets should always describe the kind of dietary protocol they are considering, the specific nutritional composition (fat, protein, CHOs), the ketogenic ratio and target level of ketosis, when ketosis is considered as a component of the mechanism of action of the diet. Moreover, a correct abbreviation should be used for it.

We propose to adjust the abbreviations in VLCHKD for Very Low CarboHydrate Ketogenic Diet and VLEKD for Very Low Energy Ketogenic Diet to clarify the differences in dietary composition.

Declaration of competing interest

The authors declare the absence of any commercial or financial interest that could be construed as a potential conflict of interest.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.numecd.2024.01.014.

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