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Ketogenic diet in children and adolescents: The effects on growth and nutritional status

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ABSTRACT

The ketogenic diet is known to be a possible adjuvant treatment in several medical conditions, such as in patients with severe or drug-resistant forms of epilepsy. Its use has recently been increasing among adolescents and young adults due to its supposed weight-loss effect, mediated by lipolysis and lowered insulin levels. However, there are still no precise indications on the possible use of ketogenic diets in pediatric age for weight loss. This approach has also recently been proposed for other types of disorder such as inherited metabolic disorders, Prader-Willi syndrome, and some specific types of cancers. Due to its unbalanced ratio of lipids, carbohydrates and proteins, a clinical evaluation of possible side effects with a strict evaluation of growth and nutritional status is essential in all patients following a long-term restrictive diet such as the ketogenic one. The prophylactic use of micronutrients supplementation should be considered before starting any ketogenic diet. Lastly, while there is sufficient literature on possible short-term side effects of ketogenic diets, their possible long-term impact on growth and nutritional status is not yet fully understood, especially when started in pediatric age.

1. Introduction

Ketogenic diet (KD) can be summarized as a reduction or interruption of carbohydrates intake resulting in metabolic changes, favoring ketogenesis in order to provide an alternate source of energy [1]. This dietetic pattern makes the ketone bodies (β-hydroxybutyrate, acetoacetate and acetone), the main source of energy instead of glucose. This process is known as "nutritional ketosis" [2,3].

KD is a high-fat, low-carbohydrate diet that has historically been used as a therapeutic intervention for pediatric patients with epilepsy due to its ability to reduce the frequency and severity of seizures. KDs have also been proposed for other conditions such as cancer, obesity and various genetic neurological and metabolic disorders. The benefits of a KD in pediatric patients include improved seizure control, weight loss, and improved insulin sensitivity. Several patterns of KD have been used for medical purposes; some of them are based on modulations of the classic KD diet, with different macronutrient ratios of fat, protein and carbs.

Most common KDs patterns include the classic KD, the medium-chain triglyceride (MCT) KD, the modified MCT KD, and the modified Atkins diet [4,5]. KDs can be based on natural foods or pre-constituted formulas, and they can be given orally or through artificial nutrition devices (nasogastric tube, gastrostomy, jejunostomy, parenteral administration). Ketogenic parenteral nutrition may be indicated when enteral intake is temporarily limited or impossible, but evidence is limited, and evidence-based prescriptions are lacking [6–8].

Abbreviations: KD, Ketogenic diet; MCT, Medium-chain triglycerides.

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In addition to its potential benefits, the KD may also pose some challenges in pediatric patients, including restricted food choices and difficulties adhering to the diet over the long-term. Short-term effects of the diet may include nausea, constipation, fatigue, dehydration, and electrolyte imbalances [9,10]. Moreover, sudden increases in carbohydrate intakes could lead to a loss of the beneficial effects of ketosis [11].

There is limited research on the long-term effects of the diet on growth and development, bone health, and cardiovascular health [12,13]. Regarding the possible impact on growth in pediatric age, few data are reported. In young adults, instead, short term KDs are becoming a common weight-loss approach [9,11,14]. Indeed, long-term effects of the diet are less clear and then require further investigation. Constant monitoring is necessary for all patients on a KD, and, even when used for short periods, it should always be implemented under medical supervision to ensure proper monitoring and management of potential adverse effects [15].

Despite these challenges, the KD remains an effective therapeutic option for pediatric patients with epilepsy and other conditions, when implemented correctly and monitored closely by healthcare professionals. These diets have been shown to reduce seizure frequency and severity, improving insulin sensitivity and weight loss. KD has long been known as a possible approach to various purposes, due to its potential beneficial effects on specific disorders, in addition to its effect on weight loss [16,17]. More knowledge about the long-term effects of KD on nutritional status might lead to expand the use of this dietetic pattern, thanks to its beneficial effects and potential therapeutic role. Indeed, some concerns about the possible long-term consequences (e.g., increase in cholesterol and triglyceride levels, growth disorders) and the low palatability have limited the KD use in clinical practice [18–20]. Further research is needed to better understand the potential long-term effects of the diet on pediatric patients, even if it should be considered a valuable tool in improving health outcomes in specific cases.

The aim of this review is then to analyze the current evidence about possible short- and long-term effects of KD on growth and nutritional status in pediatric age.

2. Material and methods

This narrative review was performed by a comprehensive search of the literature using the following electronic databases: Pubmed/Medline, Embase and Web of Science. Two authors independently identified the most relevant studies, including original papers, meta-analyses, clinical trials and reviews about ketogenic diet published in English since January 2002 up to December 2022. Literature on adult and pediatric populations was considered and, regarding pathogenetic mechanisms, preclinical studies were also included. The search was performed using following keywords (alone or in combination): ketogenic diet, nutritional status, pediatric ketosis, drug-resistant epilepsy, infants, metabolic, ketones, vitamins and mineral deficiency, bone health, adherence, autism spectrum, obesity, cardiometabolic risk, lipids metabolism, atherogenic risk. To improve our search results, we also consulted reference lists from most relevant publications. We therefore conducted a specific search on studies evaluating the impact of KD on growth using the following string: (ketogenic diet) AND (nutritional status OR growth) AND (pediatric). Results of this search are given in the supplementary material. Emphasis of this narrative review was placed on studies conducted on infants, children and adolescents. Data were extracted based on their relevance to the topic.

3. KD indications in pediatric age

Fig. 1 describes main mechanisms of action of KD that involve cell's function, central nervous system, gut microbiota and metabolism.

Table 1 summarizes main indications and uses of KDs that have been proven or hypothesized as a possible effective adjuvant treatment.

3.1. KD for epilepsy and other neurologic disorders

KDs induce metabolic changes that mimic a starving state [47]. Significant changes in plasma levels of free fatty acids, insulin, glucose, and ketone bodies can be observed within a few hours [48]. When they penetrate the blood–brain barrier, crossing the blood brain barrier, ketone bodies (acetoacetate, acetone, and beta-hydroxybutyrate) can exert an anticonvulsant effect [49]. Moreover, KD is linked to elevated levels of gamma-aminobutyric acid (GABA), mitochondrial biogenesis, oxidative phosphorylation, reduced neuronal excitability and firing, and stabilized synaptic function. The ATP production enhanced by KDs, together with a reduced brain glucose consumption, seem to induce ATP-sensitive potassium channels, increasing the seizure thresholds. Decreased glutamatergic synaptic transmission and suppression of the

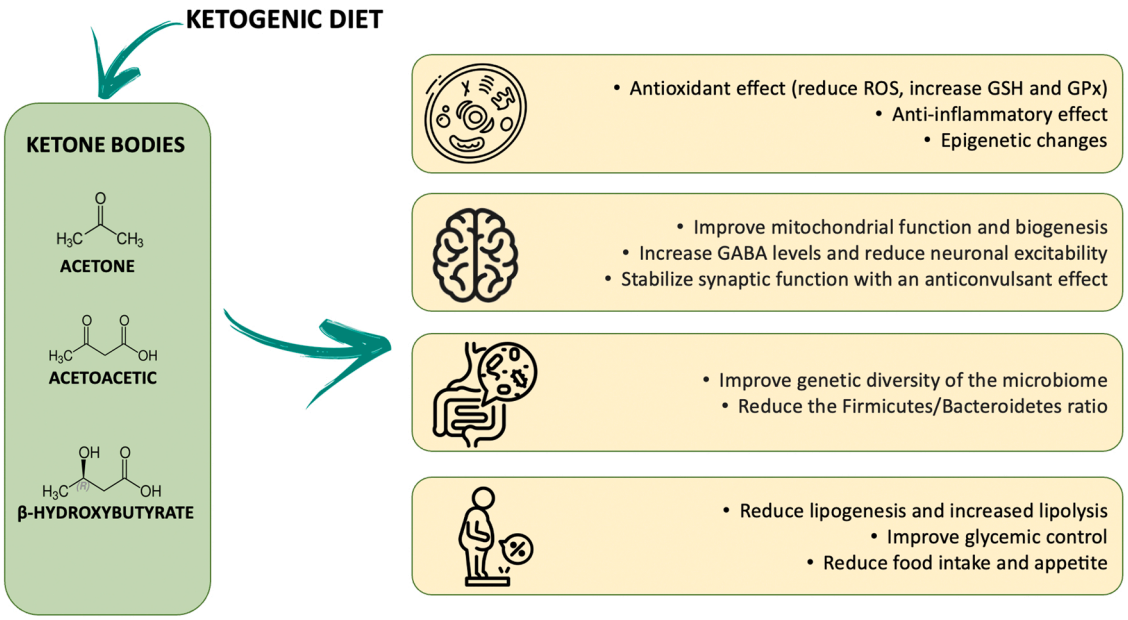

Fig. 1. Ketone bodies effects on human body. Abbreviations: Reactive oxygen species (ROS); Glutathione (GSH); Glutathione peroxidase (GPx); Gamma-aminobutyric acid (GABA).

Table 1
Possible indications of KD in pediatric age, with relative evidence.

Children and adolescents	Indications
1) Inherited metabolic disorders	• Glucose transporter protein 1 (GLUT-1) deficiency[21] • Pyruvate dehydrogenase deficiency (PDHD) [22] • Complex 1 mitochondrial disorders[23] • Glycogen storage diseases (type III and VI)*[24] • Others (phosphofructokinase deficiency, argininosuccinate lyase deficiency, adenylosuccinate lyase deficiency)*[25]
2) Epilepsy	• Myoclonic epilepsy (Dravet syndrome and Doose syndrome)[26,27] • Drug-resistant epilepsy[28] • Febrile infection-related epilepsy syndrome (FIRES)[29] • Ohtahara syndrome*[30] • Infantile spasms*[31]
3) Neurodevelopmental and genetic disorders	• Prader-Willi and Angelman syndromes*[32,33] • Pelizaeus-Merzbacher disease*[34] • Rett syndrome*[35] • Tuberous sclerosis complex*[36] • Autism spectrum disorder*[37,38]
4) Other neurologic disorders	• Stroke*[39] • Migraine*[40] • Multiple sclerosis*[41]
5) Tumors	• Gliomas and neuroblastoma*[42,43] • Adenocarcinomas*[44]
7) Others	• Overweight and obesity*[45,46]

* Poor evidence: absence of recommendations, guidelines, meta-analyses or systematic reviews that found a proven efficacy, or when just few clinical trials or case series without univocal results have been published.

mammalian target of rapamycin pathway have also been proposed as an anticonvulsant effect of KDs [50].

Epilepsy is a neurological disorder characterized by recurrent seizure [51]. Almost one out of three patients with a diagnosis of epilepsy do not achieve seizure control despite antiepileptic drugs (AEDs) [52]. Among non-pharmacological approaches to drug-resistant epilepsy, most described options are represented by vagal nerve stimulation, surgical treatment and KD [51]. KD was introduced in treatment of epilepsy in 1921, but its use returned to the fore in recent years [53]. Other conditions known for a possible use of KDs include neurodevelopmental disorders such as autism spectrum disorder, rare neurogenetic diseases, such as Rett syndrome and Fragile X syndrome, neurodegenerative ones, such as Pelizaeus-Merzbacher disease, and other neurologic diseases, such as stroke and migraine, even still with poor evidence [39,40,54]. Recently, few cases suggested a possible role in decreasing paroxysmal activity in children affected by alternating hemiplegia of childhood [55].

Recently, KD was also proposed as a therapy for mitochondrial disease such as glucose transporter type 1 (GLUT-1) deficiency, along with glycogen storage diseases or pyruvate dehydrogenase deficiency (PDHD) [25,56–59]. As said, KD can be considered a safe and effective treatment for severe forms of seizures and epilepsy, that are common symptoms of most mitochondrial disorders, even if few data are described in the literature, and recommendations are currently weak [23].

Even if the administration of KD is mainly enteral, severe, or acute illnesses may alter the GI function or need for an exclusive parenteral feeding, as in cases of some refractory epilepsies [6,7]. A proper and safe administration of KD in neurologic patients, indeed, has recently been described with the goal of improving seizure control and reducing the risk of possible metabolic side effects [60]. A frequent problem related to the intravenous KD administration is represented by the subsequent hypertriglyceridemia and increase of hepatic/pancreatic enzyme concentrations. Moreover, circulating lipids may produce lipemic blood samples, which directly interfere with laboratory exam results [61]. According to most recent international guidelines for parenteral nutrition, the amount of parenteral lipids administered to infants should not exceed 4 g/kg per day (maximum of 3 g/kg/day for other children) [62]. Furthermore, since propofol is frequently used among these patients, its 10% lipid composition (0.1 g/ml) should always be considered for this calculation [63]. Lastly, trials conducted so far among pediatric patients with refractory epilepsy showed good safety and efficacy in maintaining seizure control [4]. This evidence have been found particularly true among infants, in whom better tolerance and efficacy have been found, and in which KD could therefore be considered not only as a last resource, but an early therapeutic approach, with better short- and long-term outcomes [64,65].

Some hypotheses have been made on a possible role of KD in pathologies such as autism and multiple sclerosis [38,66]. Although evidence is still poor, neuroprotective effects of ketones on the brain energy metabolism and GABA regulation have led to hypothesize a potential beneficial role in autism spectrum pathologies [37,67]. However, it should be emphasized that these patients are often affected by food selectivity disorders, and a restrictive dietary approach can be severely limited and difficult to be standardized [68]. Nonetheless, some authors the evidence of possible behavioral improvements after KDs in patients with autism spectrum disorder with improved socialization skills [69–71]. However, all pilot studies that have been conducted are generally on nonsignificant samples, and further long-term studies would therefore be necessary to be able to reach concrete conclusions or hypotheses.

Analogue considerations can be made for multiple sclerosis. In fact, although it has been demonstrated that a KD can reduce Reactive Oxygen Species, by modulating the activity of catalases, mitochondria and glutathione [72,73], there is no in vivo evidence on how a possible reduction in neurodegeneration can directly correlate with a clinical improvement or an evolutionary slowdown in the context of progressive multiple sclerosis refractory to therapies. Some recent pilot studies conducted on adults found how a KD may safely improve fatigue, induce weight loss and reduce serologic proinflammatory adipokines in patients [41,74].

3.2. KD for overweight and obesity

KDs are very low in carbohydrates intake, while generally high in fat, and moderate to high in proteins. This ratio may have the potential to promote weight loss and improve lipidic derangement, glycemic control, and insulin sensitivity and for these reasons it was applied in the treatment of obesity [45].

It is well known the role of KD before bariatric surgery to improve the results and to reduce perioperative risk in adults [75]. In addition to this, the prevalence of overweight and obesity has recently been shown to be steadily increasing in children and adolescents, with percentages approaching 30% in many countries [76,77]. These data have led to the creation of different dietary approaches to address the emergence of childhood obesity. Although most of authors are concerned that an unbalanced diet with a low intake of carbohydrates and a high intake of fats and proteins could be harmful in childhood, some studies have shown its effectiveness in absence of significant negative effects [20,78]. Nonetheless, recent reviews highlighted the benefits of KDs on weight loss with encouraging data [10,79,80], and some studies conducted on patients on KD have found a positive reduction in triglycerides, cholesterol and blood pressure levels, with an increase in high-density lipoprotein (HDL) cholesterol [81,82]. The reduction of appetite related to a KD and its effects on the neurotransmitters that regulate the sensation of hunger, together with the effect promoted by the ketones themselves could underlie these findings [14,83].

Finally, it has been hypothesized that the results of a KD could be related to its role in the metabolism of fats, with an increased consumption of lipids and triglycerides and a consequent massive lipolysis [1,84]. Moreover, KD may have a positive effect on gluconeogenesis

[85]. To date, few data regarding KD in the treatment of obesity in pediatric age have been reported. Encouraging data found that a specific version of low carbohydrate high fat diet may represent a safe dietary intervention for a selected subset of pediatric obese patients who are trying to lose weight and did not respond to dietary and lifestyle changes [86]. To date, very low- and low-carbohydrate approaches have been suggested to be beneficial for selected adolescents with prediabetes, insulin resistance, or nonalcoholic fatty-liver disease (NAFLD) or polycystic ovary syndrome (PCOS), who have difficulty reducing weight after nutritional counselling [87,88].

However, both the difficulty of implementing this type of diet in a child's daily life (lack of acceptance of certain foods, poor palatability, meals outside the home to be managed by parents, negative side effects), with implications in social life, as well as the cost of the diet on the family, are factors that limit this type of approach, and the dropout rates are high [45,86,89].

Lastly, a recent cross-sectional descriptive study investigated the role of KD in children with Prader-Willi Syndrome [32]. Ten patients with a median age of 52.5 months followed a KD for an average of 16.5 months. All patients with obesity had a significant weight loss and appetite reduction after one month of treatment. No side effects were reported in any patients, except for mild hypercholesterolemia in 6 patients. All families reported that sleep problems were improved, and the two patients with epilepsy had a significant improvement in symptoms. These findings suggest that an appropriate approach with a low-calorie, carbohydrate-restricted, diet and close monitoring can have a positive effect on the weight control of individuals with syndromic forms of obesity.

3.3. KD in cancer management

Even if cancer may seem a rare disease in childhood and adolescence (1 out of 6500), its incidence has risen in recent years, while new therapeutic approaches have improved the survival rates [90,91].

The Warburg effect has been described as the hypothesis that cancer cells have an almost exclusive glucose-dependent metabolism, with a consequent use of lactic acid even in aerobic conditions [92]. Due to the Warburg effect, the KD is recently used as an adjuvant treatment to starve cancer cells, making them more vulnerable to chemotherapy and radiation [93].

KD can starve the cancer cells by reducing their ability to utilize glucose, while normal cells can adapt and begin utilizing ketone bodies for their energy demands. Another potential benefit could be the decrease in insulin that results from being in nutritional ketosis, which would reduce insulin-like growth factors that support cancer proliferation [94]. Another mechanism suggested is that decreasing blood glycaemia and increasing the concentration of ketones an inhibition of the NLRP3 inflammasome, which has a central role in cancer pathogenesis, could be reached [95]. KD seems then to have beneficial effects when used as an adjuvant with other therapies and when administered soon after the diagnosis [10,96].

Although the data are comforting in preclinical studies of xenograft murine models, a recent systematic review and meta-analysis of randomized controlled trials concluded that there is inadequate evidence to support the beneficial effects of KD on antitumor therapy [97].

Even if no clinical trials on children have been conducted yet, some preclinical data found an enhanced anti-tumoral effect in neuroblastomas and gliomas through a combination of chemotherapy and KD [98]. KD was contraindicated in BRAF V600E mutation-positive tumors, and hypoglycemia-prone-patients like those with diabetes mellitus [43]. Moreover, it has been suggested that the subsequent suppression of the insulin feedback could enhance the efficacy of PI3K inhibitors, with possible beneficial effect on the acute myeloid leukemia treatment [99]. However, in five pediatric patients with tuberous sclerosis complex, Chu-Shore et al. found how KD did not induce tumor regression or growth suppression [100].

Lastly, some studies have suggested a possible impact of KD in the management of colonic, pancreatic and breast carcinomas in adults, and new combination therapies based on KD and conventional therapies are under consideration [80,101–104].

3.4. KD in patients with diabetes type 1

Since a low-carbohydrate diet may potentially cause poor linear growth, increased metabolic risks, poor bone health and mineral deficiencies, a carbohydrate restriction is typically not recommended in patients with type 1 diabetes (T1D) [105]. Additionally, diets high in unsaturated fats and low in fibers have been linked to a worsen glycemic control among children and adolescents with T1D. Moreover, ketoacidosis, hypoglycemia, dyslipidemia, and glycogen depletion are typical events that may occur in patients with T1D [106].

Nonetheless, frustration with glycemic outcomes has led to a resurgence in interest in low-carbohydrate diets. Low-carb diets have not yet been thoroughly investigated in the treatment of T1D. Several case reports indicate that ketogenic diets have successfully improved seizure control and cognitive function in children with T1D and epilepsy while meeting glycemic targets [107–110].

Recently, a clinical protocol to safely manage children with T1D on low-carbohydrate or KDs who had concomitant diseases has been published [111], and Seckold et al. published a review on how to monitor T1D children on KDs to ensure a metabolic and nutritional safety [106]. However, most trials conducted on diabetic patients and evaluating the glycemic outcomes of low-carbohydrate diets are cross-sectional and on adults, without control groups or validated dietary information [112]. Participants were also highly motivated, mostly self-selected individuals who used stringent glycemic objectives with additional insulin corrections and daily blood glucose monitoring as part of their intensive insulin control regimens. Due to these issues, it is challenging to determine the extent to which a dietary carbohydrate restriction impacts on glycemic outcomes, and the use of KDs on pediatric patients with T1D is still debatable.

4. Impact on nutritional status

4.1. Growth

As all other dietary treatments in children, one of the main goals of KD is to support growth in accordance with the genetic target, relieving symptoms and avoiding malnutrition. In literature, studies on the effect of KD on growth in children mainly involve neurologically impaired children with drug-resistant epilepsy and discussion on the role of KD in growth is still open. Liu et al. recruited 25 neurological children fed with classic KD or MCT KD to evaluate growth, nutrient intake and biochemical markers after 4 months of treatment [113]. They found statistically significant increases in height in both groups, but not in the percentiles of height and age. On the contrary, weight percentiles fell by about 10 percentiles in all children. Another study involving 24 children (10 with cerebral palsy) aimed to evaluated long term effect on growth, body composition and resting energy expenditure (REE) at baseline, after 3 and 15 months of KD, compared to 75 healthy children [114]. After 15 months of treatment, linear growth status declined while weight status and REE were unchanged. REE remained reduced in children with CP.

Armeno et al. found that most of the 45 recruited children with refractory epilepsy after 24 months of KD had achieved proper growth, with an improvement of their nutritional status [115]. Standard deviation scores were calculated at KD initiation and at a two-year follow-up. At KD start, BMI was normal in 55% of the patients, while underweight was observed in the 25%, and overweight/obesity in the 20%. After 24 months of follow-up, 73% of the patients had a normal BMI, 16% were underweight, and 11% were overweight/obese. After 24 months of treatment, a decrease in linear growth was found only in 4 patients.

Ferraris et al. found that most children (80%) treated with KD did not present growth retardation after 12 months [116].

Considering patients with GLUT-1 deficiency, Bertoli et al. found that children under the age of 10 had a higher prevalence of stunted growth than their healthy peers, while 20% of them were underweight at birth in absence of a stature deficiency [117]. No distinguishing characteristics of body composition were found in their study, and no patients exhibited stature deficiencies. No correlation between growth failure and the glycemia and glycorrhachia ratio was found.

According to these mixed results, a strict follow-up for children on KDs is necessary to ensure a linear growth. Further study may be necessary to investigate and to identify predictive factors that can affect growth mechanisms. Table 2 sums up recent studies concerning possible impact of KDs on growth and nutritional status.

4.2. Vitamin and micronutrient status

Among patients on KD, vitamin and mineral deficiencies have been described, and a supplementation with multivitamins may then be indicated [124–126]. Some cases of pellagroid dermatitis, thiamine deficiency and neuropathies have been reported [127–129]. A further supplementation with carnitine may be necessary too [130]. KD seems to not provide enough content of folate, calcium, and magnesium, and it has been shown that even after starting a supplementation, micronutrient level remains inadequate in most patients [124]. The different protocols, as well as the presence of underlying deficiencies, comorbidities and different baseline features of patients, might contribute to these findings. Such treatments usually improve the concentration of many micronutrients but fail to provide a complete supplementation, and therefore a more tailored approach is warranted.

Moreover, copper deficiency associated with neutropenia and anemia has been reported [131,132]. Selenium levels have been found to be significantly lower in epileptic patients on KD, and a daily supplementation for this micronutrient has been suggested [133,134]. Indeed, cardiologic disorders such as cardiomyopathy and ST-segment-elevation have been described, and the mechanism underlying these cardiac alterations has been associated with selenium deficiency [135,136]. Selenium and cooper blood levels should then closely be monitored before and during KDs administration. Indeed, a tailored therapeutic approach is needed among these children to avoid deficiency that can be difficult to predict before starting diet. For these reasons, at the moment, there are no therapeutic doses proposed for micronutrients supplementation in children on KD.

4.3. Bone health

Long-term follow-up studies conducted on epileptic children on KD found an increased incidence of bone fractures and decreased bone mineral density [137–139]. Reasons for this data need to be evaluated: chronic ketoacidosis causes an increased demand on bone minerals for buffering capacity and decreases renal conversion of 25(OH)D to 1,25 (OH)D [140].

A key role may be played from acidosis: since ketone bodies are acids, serum bicarbonate level is often below its normal range in these patients, probably due to an insufficient production or increased need during KD [137]. Moreover, an elevated urinary calcium-creatinine ratio in absence of hypercalcemia has been found [138]. These data could be the cause of kidney stones that occur in approximately 1 out of 20 patients on KD [140,141]Bone mass density (BMD) seems to be decreased during KD, but it is not yet clear which patients are most at risk of osteopenia. Simm et al. found that patients who are able to walk have a significantly higher decline in BMD when compared to non-ambulant children [138]. A positive effect of intravenous bisphosphonate therapy has been observed in this group of patients [139].

A specific protocol at the beginning of a therapeutic KD and during

Table 2
Studies evaluating the effects of therapeutical KD on growth of patients with neurological disorders.

First author, year	Population	Diet	Outcome
Liu YM et al., *2003* [113]	25 children with intractable epilepsy	Classic or MCT KD diet for 4 months	Both groups had statistically significant height increases of 2–3 cm but did not have significant increases in height/age percentiles. Weight percentiles decreased by approximately 10 percentiles for both diets.
Groleau et al., *2014* [114]	24 children (10 with cerebral palsy) 75 healthy children	KD for 3 and 15 months	After 15 months of the ketogenic diet, linear growth status declined while weight status and REE were unchanged. REE remained reduced in children with CP.
Tagliabue A et al., *2012* [118]	18 patients with medically refractory epilepsy	KD for 6 months	No statistically significant differences at 6 months in terms of height, weight, BMI z-scores, and REE.
Armeno et al., *2019* [115]	45 children with refractory epilepsy	KD for 24 months	Growth deceleration was observed in 9% of the patients. However, the nutritional status was maintained or even improved.
Ferraris et al., *2019* [116]	34 children with drug-resistant epilepsy (n = 14) or GLUT-1 deficiency (n = 20)	KD for 12 months	Growth retardation may occur in a minority of children treated with the KD.
Kim JT et al., *2013* [119]	40 children with epilepsy	KD for 2 years, with 1 year of follow-up after discontinuation	Significant reduction in both height and weight gain among children with epilepsy after prolonged KD was found. After a year of diet discontinuation, significant catch-up growth was evident in both height and weight.
Vining et al., *2002* [120]	Prospective cohort study of 237 children with intractable epilepsy	133 children KD for 1 year 76 for 2 years	The KD generally provides sufficient nutrition to maintain growth within normal parameters over a defined period.
Neal EG et al., *2008* [121]	75 children with intractable epilepsy	Classic or MCT KD for 3, 6, and 12 months	Both weight and height z scores decreased during diet treatment. By 12 months, there was no difference in outcome between classic and MCT KD protocols despite the increased protein in the latter diet.
Peterson SJ et al., *2005* [122]	57 patients (1–26 years old) with intractable epilepsy	KD for 6, and 12 months	Subjects on the ketogenic diet showed a delay in growth.
Ruiz Herrero J et al., *2020* [123]	26 children with drug-resistant epilepsy	Children who have been treated with a KD for more than 2 years	The KD significantly affected height after 2 years of treatment.

* All studies found KD to be safe, with no adverse events observed.

the follow-up should then be performed, with a close monitoring of BMD and an abdomen ultrasound for kidney stones. An eventual prophylactic prescription of calcium, vitamin D and oral potassium citrate has been recently suggested [142].

It is important to highlight that studies on bone health and KD were conducted only in children with epilepsy. Indeed, many antiepileptic drugs can negatively affect bone health and induce bone loss both directly and indirectly [143]. Directly, some AEDs such as phenytoin, phenobarbital, and carbamazepine can decrease vitamin D levels, which can lead to decreased calcium absorption and bone mineralization [144]. Additionally, these drugs can increase the production of the enzyme alkaline phosphatase, which can lead to increased bone turnover and resorption [145]. This results in a decrease in bone density, making bones more brittle and prone to fractures.

Indirectly, AEDs can affect bone health by inducing changes in hormonal levels [146]. For example, valproic acid can increase levels of prolactin, which can lead to decreased levels of estrogen in women. Decreased estrogen levels can lead to increased bone resorption and decreased bone density. Similarly, AEDs such as carbamazepine and phenobarbital can induce the cytochrome P450 enzyme system, which can increase the metabolism of estrogen and testosterone, leading to decreased levels of these hormones and subsequent bone loss [147]. In addition to these direct and indirect effects, AEDs can also have negative effects on bone health by inducing vitamin D deficiency and impairing calcium absorption.

Overall, the negative effects of AEDs on bone health and bone density are a significant concern for individuals with epilepsy. Patients taking AEDs should be monitored closely for changes in bone density, and a screening by DEXA should be performed in these children who have followed a KD for a long time [148,149]. Appropriate interventions could be taken to prevent bone loss and reduce fracture risk. This may include calcium and vitamin D supplementation and, when possible, weight-bearing exercises and lifestyle modifications to reduce fracture risk factors [144,145].

4.4. Cardiometabolic alterations

Metabolic disorders such as dehydration, hypoglycemia, symptomatic ketosis and acidosis are some of the most common side effects of KDs [80,150]. Dehydration is more frequently observed in protocols including long fasting periods [151]. Hypertriglyceridemia, hypercholesterolemia (particularly low-density lipoprotein (LDL), and increased apolipoprotein B levels frequently occur in patients following a KD, as it has been proven in many studies [152–156].

Recent data show that triglyceride and HDL cholesterol levels generally improve during KD, but there is a variable response in LDL cholesterol levels, with some individuals experiencing a dramatic increase, particularly those with underlying genetic dyslipidemias [157]. Nonetheless, long-term effects of dyslipidemia on the development of atherosclerosis are not fully understood. There are no data proving some negative effects on the carotid intima-media thickness after a 12-month diet. However, ultrasound cardiac evaluations using a Doppler study can be useful in the presence of chronic dyslipidemia to identify any early sign of cardiovascular disease. A high intake of unsaturated fatty acids, along with the supplementation of MCT oil and carnitine may be indicated in the type of KD to be administered, while lower ratio of lipids/proteins intake may be useful in preventing the risk of dyslipidemia [130,158,159].

When KD increases dyslipidemia, it is advised by dietary guidelines for the treatment of epilepsy to adjust the fat composition by increasing the polyunsaturated fatty acids [160]. However, the use of KD does not exclude the use of anti-epileptic drugs. In patients receiving both dietary and pharmacological treatment, higher levels of cardiovascular markers (LDL cholesterol, homocysteine, apolipoprotein B, apolipoprotein B/apolipoprotein A1 ratio) were found [161]. A narrative review reported the impact on lipoproteins and oxidative stress among epilepsy children treated with KD [162]. Authors highlight that both the total and LDL cholesterol increased regardless of the timing of the intervention, potentially with a later beginning. However, the different study designs, the different types of diets and dyslipidemia cut-offs, together with the small sample size, place several limitations on their conclusions. Nevertheless, it's plausible that KD acts as an antioxidant in the central nervous system but causes oxidative stress in the peripheral system, which results for a negative clinical prognosis. Therefore, the need to create an international protocol to keep track of children receiving KD therapy for their cardiovascular health is recommendable, with a particular emphasis on oxidative stress, physical characteristics of lipoproteins, and lipid profile. Lastly, Neves et al. summarized the evidence regarding cardiometabolic risk in adult patients with drug-resistant epilepsy treated with KD [163]. Concerning the lipid and glycemic profile and vascular function in KD, they state that there are conflicting data in the literature but is crucial to monitor lipid and glucose profile biomarkers from the beginning of treatment to anticipate any adverse effects. They suggest assessing cardiovascular risk using one of the most common tools, the Framingham score [164]. This score is obtained according to several analyzed variables (blood pressure, dyslipidemia, age, sex, presence of diabetes mellitus, and smoking); it represents a percentage of the likelihood that a cardiovascular incident will occur during the following 10 years. Although these tools look valuable, they are suitable for the adult population. In the pediatric patient undergoing KD treatment, often an underlying neurological disease occurs, hence a reduced motility and/or tube feeding presence may alter these evaluations. Cardiometabolic alterations should be considered among these patients, especially in those who take anti-epileptic drugs [165]. However, to date, in pediatric patients who follow a KD as dietary treatment, no longitudinal data assessing any cardiovascular risk have been reported.

Recent findings on cardiometabolic health in neurologically impaired children highlight that even in presence of lower weight or malnutrition, a metabolic derangement can be observed. A retrospective study recruited 63 pediatric patients (11.4 ± 4.0 years) with severe disabilities, evaluating their fasting blood glucose (FBG), fasting insulin and triglycerides [166]. In this study, insulin resistance was found related to both the homeostasis model assessment for insulin resistance (HOMA-IR) and the triglyceride-glucose index (TyG index), calculated as the natural logarithm of [fasting triglycerides (mg/dl) $\times$ fasting plasma glucose (mg/dl)/2]. Moreover, impaired insulin sensitivity, pathological TyG index (>7.88) and elevated FBG were observed, respectively, in 41.3%, 63.5%, and 11.1% of patients. Another retrospective and multivariate analysis between biochemical, anthropometric and body composition data on 44 neurologic patients and 120 healthy controls found that insulin resistance is an early metabolic factor that may have an impact on the degree of metabolic involvement [167]. It's important to consider how insulin resistance affects the course of lipolysis and skeletal muscle atrophy [168]. To avoid the onset of total metabolic syndrome and the alteration of body composition, a yearly screening with tools such as HOMA-IR and TyG index should be advised in patients with an increased risk. Indeed, at-risk neurological populations may benefit from early screening for insulin resistance and/or surrogate markers of insulin resistance to reduce the risk of future cardiometabolic complications.

In Fig. 2, we summarize organs that can be involved for possible side effects of a KD, and why a specific attention is needed from clinicians.

5. Management and follow-up of pediatric patient on KD

According to all these mixed results, strict follow-up in children on KDs is necessary to ensure proper growth. The standard growth assessment should include weight, height (or tibial length in children with

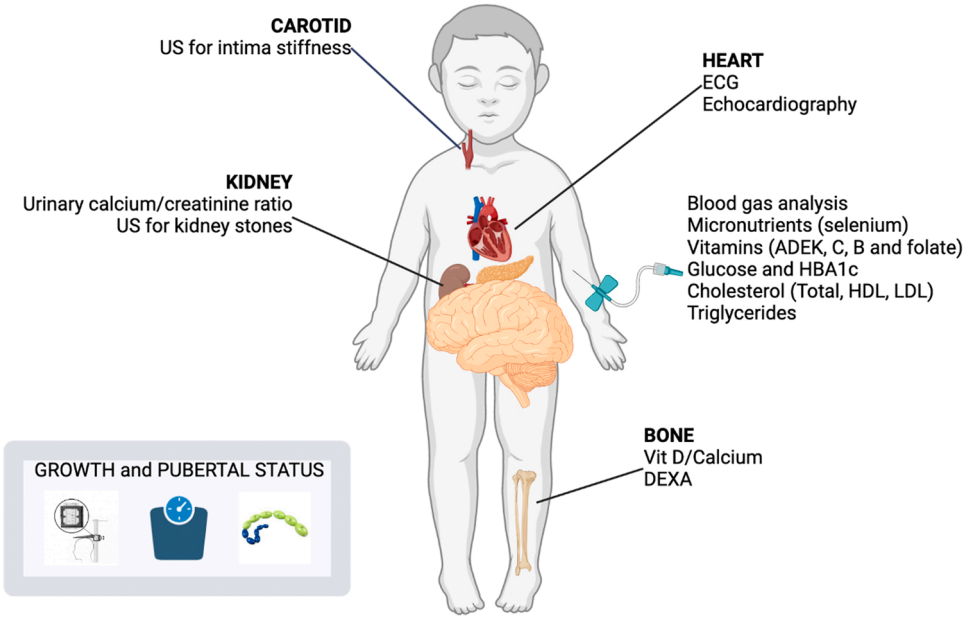

Fig. 2. An overview of principal organs to be monitored in patients on KD.
Abbreviations: Ultrasounds (US); Dual energy X-ray absorptiometry (DEXA); High-density lipoprotein (HDL); Low-density lipoprotein (LDL).

neurological impairment), BMI z-scores, mid-upper arm circumference (MUAC), waist circumference and Triceps Skinfold Thickness according to World Health Organization growth charts [169]. Moreover, to better assess the body composition, bioelectrical impedance analysis (BIA), air-displacement plethysmography (Bodpod), and Dual energy X-ray Absorptiometry (DEXA) could be considered as more reliable methods to be repeated and compared over time to monitor nutritional status after starting dietary treatment [170]. However, depending on the patient's motor level, it is necessary to choose the best detection method. In addition, it must be remembered that below certain age, there are no reference values for the pediatric population (e.g., in bioimpedance reference value <6 y) or some examinations may not be easy to perform.

Even if the administration of KD is mainly enteral, severe, or acute illnesses may alter the GI function or need for an exclusive parenteral feeding, as in cases of some refractory epilepsies. A proper and safe administration of KD in epileptic infants, indeed, has recently been described in an international consensus [171], with the goal of improving seizure control and reducing the risk of possible future metabolic side effects. A frequent problem related to the intravenous KD administration is represented by the subsequent hypertriglyceridemia and increase of hepatic/pancreatic enzyme concentrations. Moreover, circulating lipids may produce lipemic blood samples, which directly interfere with laboratory exam results.

A strict monitoring of micronutrients and vitamins allows the creation of individually tailored supplementation protocols. Some guidelines have been proposed for the clinical management of patients undergoing

AT BASELINE	Complete blood examination (EGA, micronutrients, vitamins)	ECG Echocardiography US for intimal stiffness	Urinary Ca/Creat ratio US for kidney stones DEXA	WEIGHT/HEIGHT BMI z-score MUAC
EVERY 3 MONTHS	EGA Vitamins Lipid and glucose profile	ECG	Urinary Ca/Creat ratio	WEIGHT/HEIGHT BMI z-score MUAC
EVERY 6 MONTHS	Micronutrients	Echocardiography	US for kidney stones	
EVERY YEAR		US for intimal stiffness	DEXA	HOMA-IR TyG Index

Fig. 3. A proposal for baseline screening and follow-up program in patients on KD, based on current guidelines [26,171]. Abbreviations: Blood gas analysis (EGA); Ultrasounds (US); Dual energy X-ray absorptiometry (DEXA); Mid-upper arm circumference (MUAC); calcium/creatinine (Ca/Creat).

a KD [26,171]. Fig. 3 summarizes a proposal of follow-up management, based on current evidence and these guidelines.

6. Conclusions

In this review we tried to resume different indications of KD in pediatric age and the current evidence on its possible impact on the nutritional status. Even if it is known that KD may be an effective alternative therapy in patients with drug-resistant epilepsy and considering that its use is common in adolescents and young adults as a weight-loss treatment, a clinical evaluation of possible its side effects with a strict evaluation of growth and nutritional status is essential in all patients following a KD in order to avoid possible malnutrition and ensure a linear growth. Micronutrients should be frequently monitored to avoid possible deficiencies. To better monitoring the possible cardiometabolic risks, especially in patients on enteral nutrition, the insulin resistance and/or surrogate marker of insulin resistance index should be considered during follow-up visit in order to monitor cardio-metabolic status and identify any risk at an early stage. Further studies are needed to investigate possible long-term effects of these diets when started in pediatric age.

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CRediT authorship contribution statement

Elvira Verduci, Antonella Diamanti, Gianvincenzo Zuccotti: Conceptualization. **Antonio Corsello, Chiara Maria Trovato**: Methodology. **Antonio Corsello, Chiara Maria Trovato, Elisabetta Di Profio, Sabrina Cardile**: Investigation, Writing – original draft preparation. **Elvira Verduci, Antonella Diamanti, Antonio Corsello, Chiara Maria Trovato**: Writing – review & editing. **Antonella Diamanti, Elvira Verduci, Cristina Campoy, Gianvincenzo Zuccotti**: Supervision. All authors have read and agreed to the published version of the manuscript.

Conflicts of interest

The authors declare no conflict of interest.

Data availability

No data was used for the research described in the article.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.phrs.2023.106780.

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