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REVIEW PAPER

# Physical Activity, Ketogenic Diet, and Epilepsy: A Mini-Review

Maria Ruberto[1], Vincenzo Monda[2], Francesco Precenzano[3], Girolamo Di Maio[4], Antonietta Messina[2], Valentina Lanzara[3], Eugenio Merolla[3], Nicola Tartaglia[5], Antonio Ambrosi[5], Marcellino Monda[2], Cristian V. Francavilla[6], Giovanni Messina[7], Fiorenzo Moscatelli[7]

[1]Centro Minerva pro-Juventute, Naples, Italy, [2]University of Campania Luigi Vanvitelli, Department of Experimental Medicine, Section of Human Physiology and Unit of Dietetic and Sport Medicine, Naples, Italy, [3]University of Campania Luigi Vanvitelli, Department of Mental Health, Physical and Preventive Medicine, Clinic of Child and Adolescent Neuropsychiatry, Naples, Italy, [4]University of Naples Federico II, Department of Experimental Medicine, Naples, Italy, [5]University of Foggia, Department of Medical and Surgical Sciences, Foggia, Italy, [6]University of Enna "Kore", Enna, Italy, [7]University of Foggia, Department of Clinical and Experimental Medicine, Foggia, Italy

**Abstract**

One-third of patients with epilepsy do not respond to antiepileptic drugs and may seek complementary and alternative treatment modalities. Dietary therapies, such as the ketogenic diet (KD), the modified Atkins diet, as well as the medium-chain triglyceride and the low glycaemic index diets, have been successfully implemented with some forms of epilepsy and are growing in utilization. The KD is a high-fat, low-protein, low-carbohydrate diet that has been used for various conditions for over a century. Insights into the mechanism of action of these diets may provide more targeted interventions for patients with epilepsy. Knowledge of these mechanisms is growing and includes neuroprotective effects on oxidative stress, neuroinflammation, potassium channels in the brain, and mitochondrial function. In this review, we explain the role of physical exercise and the ketogenic diet on epilepsy.

***Keywords:*** *ketogenic diet, physical exercise, epilepsy*

## Introduction

Movement is essential for physical and neurocognitive development, ensuring correct growth and giving many benefits from childhood to adulthood. In general, motor activity plays a pivotal role in psychological, educational, and social terms. Indeed, sport practice induces harmonious physical development with common significant benefits, independent of sport type. In contrast, each sport imposes rules that children learn to know and respect step-by-step, improving their social skills and cognitive abilities, because regular physical exercise has been demonstrated to beneficially affect neural health and function and reduce the risk of various neurological diseases (Monda et al., 2017a).

The practise of physical activity by subjects with epilepsy has been a matter of debate for health professionals dealing with this disease, and of concern for the patients themselves, as well as families and caregivers. A question frequently asked is if exercise could result in an increase in seizures. As physicians themselves were unable to properly counsel, they have been discouraged from participating in physical activities or sports. Persons with epilepsy must deal with many social and cultural stigmas, and restricting physical activity contributes to further limitations to normal and healthy living (Pimentel, Tojal, & Morgado, 2015).

Epilepsy is a common and prevalent neurologic disease found in 2% of the population, affecting people of all ages and characterized by a predisposition to seizures as well as neurobiological, psychological, cognitive, and social consequences (Scheffer et al., 2018). Due to their condition, patients with epilepsy may develop other medical problems, such as heart dis-

Correspondence:

G. Messina
University of Foggia, Department of Clinical and Experimental Medicine, Viale L. Pinto 1, 7122 Foggia, Italy
Email: giovanni.messina@unifg.it

ease, cognitive decline or dementia, insulin resistance, obesity, atherosclerosis, and internalizing problems, such as anxiety and depression (Fisher et al., 2014). Commonly, individuals with epilepsy tend to have a sedentary lifestyle, which leads to poor physical fitness (Capovilla, Kaufman, Perucca, Moshé, & Arida, 2016).

Consequently, individuals with epilepsy have low levels of maximal oxygen uptake and cardiorespiratory fitness and reduced levels of strength and flexibility. The lower aerobic fitness observed in people with epilepsy may be associated with their sedentary habits (Rauchenzauner et al., 2017). Physical activity should be encouraged in this group, as previous studies have reported several positive effects of physical exercise in people with epilepsy. However, the correct management and prescription of physical exercise programmes in epilepsy patients depend on health professionals' knowledge(A. Olivares, G. Olivares, Mula, Górriz, & Ramírez, 2011).

People with epilepsy (PWEs) have often been advised against participating in sports and exercise, mostly because of fear, overprotection, and ignorance about the benefits and risks associated with such activities (Tsuji, 2017). Although the implications of engaging in sports and physical exercise for PWEs have been extensively debated, several studies reported that in most cases these activities can have a beneficial influence on seizure frequency and severity (Pimentel et al., 2015). As a result, attitudes regarding sports and epilepsy have changed considerably in recent decades, as have recommendations in clinical practice (K.R. Kaufman, & N.D. Kaufman, 2013).

Epileptic events can be managed with a ketogenic diet, although it is by no means clear how ketone bodies regulate neuronal events in the brain to control the episodes. The brain utilises ketone bodies as an energy source rather than glucose with this type of diet. Many studies have been presented to explain how the ketogenic diet works physiologically in PWE, and these are covered in this review. The ketogenic diet is very effective at controlling epilepsy but is difficult to tolerate. Hence other diets, especially the low glycaemic index diet, have been developed as an alternative (Qi & Tester, 2019). The authors proposed that another option for the dietary management of seizures is to consume a very slowly digestible glucose source, which minimizes the impact on insulin response, in conjunction with a source of ketones (preferably those generated from lipid metabolism) to optimize energy for the brain and body.

*Physical exercise in PWEs*

Determining whether subjects with epilepsy can be involved in specific physical exercises or specific sports requires a careful clinical assessment of the individual risk-benefit ratio, particularly with respect to the risk of a seizure occurring during the activity and related implications. Factors to be considered include not only the type of sport and the probability of a seizure occurring, but also individual characteristics, such as the type and severity of the seizures, the consistency of any prodromal manifestations, the history concerning any seizure-precipitating factors, the likelihood of adequate supervision by family members or other personnel, and the willingness of the informed PWE (or parents) to take a reasonable level of risk (Capovilla et al., 2016). A careful medical history is essential to ascertain not only the frequency and characteristics of the seizures, but also any previous seizure-related accidents or injuries, duration of periods of seizure freedom, and degree of adherence to treatment (Pimentel et al., 2015). Therefore, choosing a specific physical exercise/sport for a person with epilepsy requires consideration of personal attitudes and preferences, health status, as well as medical advice. To this point, recommendations for the issuance of certificates of fitness for sports activities are needed. In clinical studies, exercise has been reported to be associated with reduced epileptic form discharges on electroencephalography (EEG) and increased seizure threshold (Nakken, A. Løyning, T. Løyning, Gløersen, & Larsson, 1997), and seizures are unlikely to occur during incremental physical effort to exhaustion (de Lima et al., 2011). These findings are strengthened by studies in animal models of seizures and epilepsy, in which aerobic exercise training was found to retard the epileptogenic process to reduce seizure frequency (Vannucci Campos et al., 2017), and to promote favourable plastic changes in the hippocampus (Schipper et al., 2016). These benefits can be particularly prominent for children with epilepsy, and the involvement of these children in sports activities at school should be encouraged. Social exclusion is highly prevalent in the teen years, and teens with epilepsy are generally less physically active than their healthy siblings (Wong & Wirrell, 2006).

Furthermore, regular exercise can improve cognitive function at all ages (American College of Sports Medicine, 2009), and enforcing a sedentary lifestyle can have deleterious effects and impact on psychosocial development, independence, and mental health. These observations led to the general recommendation that PWEs should engage in physical exercise programmes or sport activities that do not impose a significant risk of injury to themselves or others. Assessing the risks involved in physical/sports activity participation is a responsibility to be shared among physicians, PWEs, and parents if the person with epilepsy is a child or adolescent. A few clinical cases of seizures apparently precipitated by physical exercise have been reported, in some instances in relation to stimulus-related or reflex epilepsy syndromes (Qi &Tester, 2019; Scheffer et al., 2018; Tsuji, 2017). However, a causative link between these factors and the occurrence of seizures in some of the reported instances is speculative, and, in general, sport activities are unlikely to provoke or facilitate the occurrence of seizures.

Some online sites counselling PWEs provide recommendations regarding different sport activities, and most are quite liberal in the sports recommended. Especially for PWEs with controlled epilepsy, however, conflicting opinions exist regarding more controversial physical activities, such as sky diving, scuba diving, water skiing, climbing, hand gliding, or boxing and other contact sports. Most assert that water sports should always be performed under a trained supervisor, with a life-jacket, and that swimming should be done in supervised pools (Monda et al., 2017b). Some consider that restrictions for persons with complex partial or tonic-clonic seizures are needed even when preceded by warnings for sports, such as skydiving and scuba diving. A more radical position is the one not recommending it in general for PWE because they are life-threatening in case of the occurrence of a seizure (Monteiro, Aroca, Margarit, & Herán, 2019). While some do not limit participation, others do not recommend or counsel caution for the practice of combat sports like boxing or martial arts that may involve blows to the head.

Nevertheless, as seen in the literature from studies with boxers and other sports that might involve concussions, most of these are mild and do not preclude the development of epilepsy nor do they aggravate pre-existing epilepsy. Taking into account the articles reviewed, there seems to be currently a consensus that sports and physical activity, excluding scuba diving, skydiving, and solo hand gliding, should be encouraged for all PWEs with controlled epilepsy (seizure-free for more than one year). For higher-risk sports like climbing, cycling, horseback riding, water sports and swimming, snorkelling, among others, PWEs should practice them with a friend/ relative, or under the close surveillance of someone who knows that the person has epilepsy and how to deal with the occurrence of a seizure.

For those PWEs not well-controlled, limitations should be applied according to the seizure type and the particular sport or physical activity to be performed, always after discussing the risks, benefits and sports possibilities, and the need for suitable protective equipment with the assistant physician and with the sports professional. The practice of sports is still an individual choice and decision because no guidelines are available according to each particular frequency or type of seizures and the intake of antiepileptic drugs (AEDs). However, those that continue having seizures only at night, or always preceded by an aura enabling the halting of activity should have fewer limitations than those with myoclonic, atonic, absence, complex partial, or tonic-clonic seizures. Rice and the Council of Sports Medicine and Fitness (Fishman et al., 2017) elaborated guidance for clinicians, and they do not recommend special precautions for those with controlled epilepsy. For those with uncontrolled seizures, an individual assessment for collision, contact or limited-contact sports, and avoidance of archery, swimming, weightlifting, and powerlifting (Washington et al., 2001).

*Ketogenic Diet and epilepsy*

The ketogenic diet (KD) is a nutritional approach consisting of high-fat and adequate protein content but insufficient levels of carbohydrates for metabolic needs <20 g d-1or 5% of total daily energy intake (Paoli, Bianco, & Grimaldi, 2015; Phinney, Bistrian, Evans, Gervino, & Blackburn, 1983), thus forcing the body primarily to use fat as a fuel source. The original KD was proposed as a 4:1 lipid:non-lipid ratio, with 80% of daily energy intake from fat, 15% protein, and 5% carbohydrate. Many modifications have subsequently been introduced to the original KD, for example, lowering the lipid:non-lipid ratio or no restrictions in daily energy (in kilojoules) intake with protein and fat. The primary knowledge on the metabolic aspects of KD comes from studies conducted at the end of the 1960s (Owen et al., 1967, 1969), which determined that fasting (i.e., ingesting no or minimal amounts of food and caloric beverages for periods that typically range from 12 h to 3 wk) induces a particular metabolic state called "ketosis" (Paoli, Bosco, Camporesi, & Mangar, 2015).

Ketosis, the metabolic response to an energy crisis, is a mechanism to sustain life by altering oxidative fuel selection. Often overlooked for its metabolic potential, ketosis is poorly understood outside of starvation or diabetic crisis. Ketone body metabolism is a survival trait conserved in higher organisms to prolong life during an energy deficit or metabolic crisis. The advantages of ketone body metabolism during starvation are clear: providing an oxidizable carbon source to conserve precious glucose/gluconeogenic reserves while simultaneously satisfying the specific fuel demands of the brain. Ketone bodies, when present, act not only as respiratory fuels to power oxidative phosphorylation but as signals regulating the preferential oxidation and mobilization of fuel substrates.

In the early 20th century, French and American physicians, including Guelpa, Marie, Conklin, and Geyelin, started research on fasting and starvation as a treatment for epilepsy. It was shown that fasting is more effective in treating children than adolescents and that its efficacy decreases with increasing age. Following that, researchers explained dehydration, acidosis, and ketosis as possible mechanisms by which fasting helps in treating epilepsy (Wigglesworth, 1924). Other authors proposed that the diet that produces ketosis could also be used in the treatment of epilepsy (Sadeghifar & Penry, 2019). It was termed the "Ketogenic Diet", which was rich in fat and deficient in carbohydrates. KD was found to be beneficial over starvation in providing similar efficacy but could be used for prolonged maintenance.

Later, in 1946, diphenylhydantoin was discovered, and the focus of research shifted to the development of other AED, which were convenient to administer. Due to seizures which remained uncontrolled despite several trials of AEDs, KD regained its popularity (Bashinski, 1946). In 1972, Dr Robert C. Atkins promoted the "Atkins Diet", which consisted of high fat and low carbohydrate and produces ketosis (Dr. Atkins' diet revolution, 1973). After that, "Modified Atkins Diet" was developed in 2003 (Miller et al., 2003). These diets were more palatable and tolerable than previous ones. Subsequently, low glycaemic index treatment diet was proposed in 2005, based on the hypothesis that stable blood glucose at a lower level would result in modulation of insulin release and other metabolic effects, thus improving the incidence of seizure (Pfeifer & Thiele, 2005).

## Discussion

In general, several studies reported that physical activity has a positive influence on seizure frequency and severity (Vancampfort & Ward, 2019; Vancampfort, Ward, & Stubbs, 2019). As a result, attitudes regarding sports and epilepsy have changed considerably in recent decades, and presently, the risk of convulsive seizures during sports practice is minimal in cases of well-managed epilepsy (van Gorp et al., 2019). Evaluating the control of convulsive disease is, therefore, a key point in allowing sports for children and adolescents. In cases of well-controlled epilepsy, both team sports and contact or collision sports are allowed, with appropriate equipment, and the training of both parents and coaches. These data are not applicable in subjects with epileptic encephalopathies or cases of not-controlled seizures or pharmaco-resistant epilepsy (Janmohamed, Brodie, & Kwan, 2019).

Patients with epilepsy who wish to participate in sports represent a challenging population to counsel and manage because their condition puts them at risk for possibly life-threatening events; however, most of these risks are manageable. High-risk activities for this population include water sports and any water-related activity (Pimentel et al., 2015). The athlete with epilepsy who participates in such activities should have constant supervision by a responsible adult or a "buddy" who can provide immediate assistance and maximally reduce the risk of drowning, which is never negligible (Messina et al., 2015). The athlete's frequency of seizures is also a factor in determining whether his or her participation in high-risk activities is advisable. Patients with frequent seizures should be guided toward activities in which loss of consciousness or bodily control is not life-threatening. Athletes with known seizure disorders have not been reported to exhibit a higher incidence of seizures in comparison with their baseline frequencies when they play contact sports (Shehzad, Iqbal, Shehzad, & Lee, 2012; Vancini, Andrade, Vancini-Campanharo, & de Lira, 2017).

Collision sports associated with a higher number of and more forceful impacts resulting in a higher rate of concussions may place the brain at risk of seizures secondary to the increase in excitatory neurotransmitters during the acute phase of the injury, as has been described in animal models of brain injury (Viggiano et al., 2016). Clinical experience to date demonstrates that low-impact injuries typically seen in most competitive sports do not put athletes with epilepsy at increased risk for seizures (Fisher et al., 2014; Monda et al., 2017a; Pimentel, Tojal, & Morgado, 2015; Scheffer et al., 2018).

Regarding the effects of AEDs in sporting practise by children affected by epilepsy, in general, AEDs can slow mental processing, trigger physiologic changes, and cause imbalance and fatigue with reduced endurance, all of which negatively affect competitive performance (Chieffi et al., 2017). Consequently, athletes who notice these drops in performance may limit their compliance with these medications (Moscatelli et al., 2016; Operto et al., 2019). Appetite can also be affected by the use of medications, with anorexia causing a diminution of adequate nutrition that affects strength and endurance and increases the risk of seizures (Fishman et al., 2017; Owen, Felig, Morgan, Wahren, & Cahill, 1969; Paoli et al., 2015; Phinney et al., 1983; Washington et al., 2001).

People with chronic diseases, including epilepsy, should be encouraged to exercise, as should the general population. The mental and physical advantages of regular exercise are regarded as highly beneficial to a group that is usually sedentary, overweight, and with higher rates of depression.

Sports medicine professionals should have an understanding of epilepsy syndromes, types of seizures, medications, what to do when a seizure occurs during sports practice, the effect of physical exercise on seizures, and when restrictions are applied to the practice of sports (Pimentel et al., 2015). General physicians, neurologists and paediatricians should support the practice of regular physical exercise and inform patients and caregivers about the benefits associated with physical activity and the necessary precautions, such as protective gear.

Participation in organized sports provides many physical and psychological benefits for patients with epilepsy and can be safely incorporated into their lives (Iannone et al., 2019; Operto et al., 2019). By providing appropriate education and encouragement, a neurologist can ensure that patients are properly equipped to make the right choices and manage any complications that occur while they are participating in activities (Operto et al., 2019; Operto et al., 2020).

In conclusion, physical exercise and KD has a positive effect on epilepsy and is associated with reduced epileptic form discharges and increased seizure threshold, and seizures are unlikely to occur during incremental physical effort to exhaustion (Rauchenzauner et al., 2017). These findings are strengthened by studies in animal models of seizures and epilepsy, in which aerobic exercise training was found to retard the epileptogenic process, to reduce seizure frequency, and to promote favourable plastic changes in the hippocampus (Olivares et al., 2011).

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**Conflict of Interest**
The authors declare the absence of conflict of interest.

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