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Review

Effect of a ketogenic diet on autism spectrum disorder: A systematic review

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ABSTRACT

Autism spectrum disorder (ASD) is primarily characterized by impaired social interaction and communication, as well as restricted repetitive behaviours and interests. The utilization of the ketogenic diet (KD) in different neurological disorders has become a valid approach over time, and recently, it has also been advocated as a potential therapeutic for ASD. A MEDLINE, Scopus and Cochrane search was performed by two independent reviewers to investigate the relationship between ASD and the KD in humans and experimental studies. Of the eighty-one potentially relevant articles, eight articles met the inclusion criteria: three studies with animals and five studies with humans. The consistency between reviewers was $\kappa = 0.817$. In humans, the studies mainly focused on the behavioural outcomes provided by this diet and reported ameliorated behavioural symptoms via an improved score in the Childhood Autism Rating Scale (CARS). The KD in prenatal valproic acid (VPA)-exposed rodents, as well as in BTBR and Mecp2 mice strains, resulted in an attenuation of some autistic-like features. The limited number of reports of improvements after treatment with the KD is insufficient to attest to the practicability of the KD as a treatment for ASD, but it is still a good indicator that this diet is a promising therapeutic option for this disorder.

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Abbreviations: ASD, autism spectrum disorders; KD, ketogenic diet; CARS, childhood autism rating scale; VPA, valproic acid; SD, standard diet.

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1. Introduction

Autism spectrum disorder (ASD) is used to describe a range of neurodevelopmental conditions that share common features with autism, including impairments in communication and social interaction, as well as repetitive behaviours, stereotypies and a limited repertory of interests and activities (DSM-V, 2013). However, the aetiology of ASD is unclear, but evidence indicates that a strong genetic component and exposure to several environmental factors are involved in the pathogenesis of this disorder. It has been previously known that prenatal exposure to teratogens (Christianson, Chesler, & Kromberg, 1994), alcohol (Currenti, 2010) and viral infections (Atladóttir, Henriksen, Schendel, & Parner, 2012) are associated with an increased incidence of autism. According to the Centers for Disease Control and Prevention Report (2014), one in 68 children has been identified as having ASD in the U.S.A. In addition, ASD is nearly five times more common among boys (1 in 42) than girls (1 in 189) (CDC, 2014).

One of the most common comorbidities in individuals with ASD is epilepsy. It affects approximately 12% of these patients during childhood and 26% of patients during adolescence. There are several risk factors for epilepsy in children with ASD, including low IQ and adaptive functioning, older age, poor language skills, a history of developmental regression, and more severe ASD symptoms (Viscidi et al., 2013).

Dietary manipulations are becoming widely used approaches in the treatment of neurological disorders. A ketogenic diet (KD) consists of a high amount of fat and a low amount of carbohydrates. The reduced availability of dietary carbohydrates results in ketone bodies (3-hydroxybutyrate and acetoacetate) synthesis as an energy supply to the brain (Kossoff, Zupec-Kania, & Rho, 2009). A recent study reviewed potential mechanisms for a KD, like carbohydrate reduction, including the activation of adenosine triphosphate–sensitive potassium channels via mitochondrial metabolism and the inhibition of glutamatergic synaptic transmission, among other mechanisms (Danial, Hartman, Stafstrom, & Thio, 2013).

For patients with refractory epilepsy, the KD is an alternative or adjunctive therapeutic option and has been proven to reduce or provide full control of epileptic seizures (Kossoff, 2009; Kossoff & Hartman, 2012; Nordli, 2002). In neurological disorders characterized by neurodegeneration or metabolic defects, this diet is considered neuroprotective (Barañano & Hartman, 2008). Other non-epileptic uses of the KD have also been described in the literature, including uses in the treatment of Alzheimer's disease, migraine, Parkinson's disease and depression (Kossoff, Zupec-Kania and Rho, 2009).

While there is an established relationship between epilepsy and the KD, this dietary intervention has also been considered as a potential therapeutic strategy to ameliorate some of the ASD-associated symptoms (Napoli, Dueñas, & Giulivi, 2014). The limited number of reports of improvements after treatment with the KD, such as decreased seizure frequencies and an amelioration of behavioural deficits in humans (Evangeliou et al., 2003; Herbert & Buckley, 2013) and in animal models (Mantis, Fritz, Marsh, Heinrichs, & Seyfried, 2009; Ruskin et al., 2013), is insufficient to attest to the practicality of the KD as a treatment for ASD, but it is still a good indicator that this diet is a promising therapeutic option for this disorder. This systematic review aims to provide a comprehensive description of published clinical and preclinical studies involving ASD and the KD effects on behavioural symptoms and seizure control.

2. Methods

2.1. Search strategy

A MEDLINE, Scopus and Cochrane search was independently performed by two reviewers (K.C and L.S.F). The search was unlimited for date or language. The following search terms and strings were used: [(Disorder, Autistic) OR (Disorders, Autistic) OR (Autism, Infantile) OR (Infantile Autism) OR (Autism) OR (Autisms) OR (Autism, Early Infantile) OR (Early Infantile Autism) OR (Infantile Autism, Early) OR (Autism Spectrum Disorders) OR (Disorder, Autism Spectrum) OR (Disorders, Autism Spectrum) OR (Spectrum Disorder, Autism) OR (Spectrum Disorders, Autism) OR (Autism Spectrum Disorder)] AND [(Diet, Ketogenic) OR (Diets, Ketogenic) OR (Ketogenic Diets) OR (Ketogenic Diet)]. Articles were initially selected by an analysis of titles and abstracts, followed by a full-text reading. Kappa coefficients were calculated to assess the agreement between the properly blinded reviewers. Any disagreements were resolved by a third reviewer (I.S.P.). For analytical purposes, we only considered data germane to the topic of the present review; data regarding other outcomes were excluded.

2.2. Inclusion and exclusion criteria

Articles were considered eligible when they presented data linking ASD and treatment with the KD in humans and animal models of autism. We excluded all studies that did not explicitly present the evaluated outcome, as well as reviews, editorials, and comments.