Can The Ketogenic Diet Improve Autism Spectrum Disorder? From Perspectives on Diversity Interventions and Treatment

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Abstract. Autism spectrum disorder (ASD) is an extensive spectrum of abnormalities, inclusive of metabolic, mitochondrial, immune, inflammatory, and behavioral dysfunction in multiple parts of the body, resulting in multiple symptoms and disrupting an individual's ability to communicate, form relationships, develop life skills, explore, play, and learn. In recent years, the low-carbohydrate, high-fat ketogenic diet (KD) has gained popularity and been viewed as a promising non-pharmacological treatment for patients with ASD. Not only has this dietary regimen been successfully used in treating pediatric epilepsy, one of common co-occurring ASD symptoms, for over a century, but some studies have also been shown beneficial effects in lessening various other comorbid disorders (e.g., seizures and mood disorders) and behavioral deficits. This article's major objective is to briefly retrospected the literature pertaining to the feasibility and the efficacy of dietary/nutritional interventions in treating ASD-related conditions, including KD and probiotics intakes, along with behavioral therapies, consisting of applied behavior analysis (ABA) and cognitive-behavioral therapy (CBT).

Keywords: Autism Spectrum Disorder; Ketogenic Diet; Behavioral therapies; Depression; Gastrointestinal Issues.

1. Introduction

1.1. Autism spectrum disorder (ASD)

Autism spectrum disorder (ASD) include a heterogeneous set of neurological developmental disorders, with the early onset at birth in 70% cases and before 3 years of terogeneousages in 30% cases [1]. This disorder is marked by a complex range of deficits in forming social relationships, communicating through speech or voice, interpreting facial expressions, recognizing and understanding social cues, having fixated interests in a certain object, subject and activity, being preoccupied with stereotypic body movements and ritualistic behaviors, frequently accompanied with various neurological/psychiatric and somatic comorbidities [2]. Autism affects 1 in every 36 children in the US [3]. Some may exhibit at any time during their development while others may appear later in adolescence or adulthood. It is thought that environmental as well as genetic elements account for impeding the growth of children with this disorder [4]. Thus, with a view to highlighting underlying etiologies and better understanding psychological and medical needs of this population, the comprehensive review of a comorbidity burden among patients with autism is necessary.

1.2. Autism comorbidities

72% of children with autism are diagnosed with a comorbid condition [5]. Autism spectrum disorder is often complicated by epilepsy, seizure disorders, gastrointestinal (GI) issues, difficulty falling asleep, inflammation, oxidative stress, immune system dysfunction and mitochondrial dysfunction [6,7]. With numerous physically conditions and behavioral challenges, this population tend to develop comorbid mental conditions (e.g., anxiety, depression, eating disorders, etc.) later in their adolescence and adulthood, which can complicate the pathology and affect the outcome of its diagnosis and treatment [7,8]. Despite no cure available for autism, there are still conventional treatments, some of which are efficacious for reducing autism-related symptoms, including nutritional therapies, dietary therapies, and behavioral therapies [7].

1.3. The rationale for the use of the KD

The KD is a dietary strategy for obtaining a majority of energy in body from fats and consuming as few carbs as possible so that the body produces more ketone bodies like acetoacetate, acetone and β-hydroxybutyrate and so on and causes the metabolic state called ketosis [9]. Ketosis is typically attained by either abstinence from specific food categories or for health purpose or engaging in the practice of carbohydrate restrictions. Special attention should be paid to differentiate between the diet of low carbohydrate and the low-carb ketogenic diet (LCKD). Though a low-carb diet in consuming 50 to 150g in a daily carbohydrate is lower than average "Western diet", the amount is still not small enough to induce ketosis, causing the body to burn stored fat for energy, and the body won't start feeding on fat instead of glucose until a patient consumes less than 50g of carbohydrates daily [10]. The creation of ketone bodies occurs whenever lipids are used as the predominant fuel source in the liver, a procedure known as ketogenesis. There are three primary types of ketone bodies generated and used by the body for energy in the ketosis's period and all mitochondria-containing cells, including the brain and muscle, can satisfy their energy needs with ketone bodies [10]. As a result, the ketogenic diet is abundant in fats rather than carbs and the consequent limitation on carbs decreases the levels of glucose in the blood, and the following insulin alterations direct the organism to switch from a fat storage to a fat-oxidizing state and creating ketone bodies. Based on several literature investigations into mechanism of action indicate that the ketogenic diet is efficacious in improving epilepsy symptom as well as the digestive, nervous, immune, and metabolic systems and has promising therapeutic effects in behavioral improvements in children with ASD [7,11]. It has been demonstrated that the KD reduces inflammation, regulates many neurotransmitter systems, strengthens brain networks and bridges the energy gap created by cerebral glucose hypometabolism by modulating both the central and peripheral immune systems, as well as raising glutathione levels in the brain which is benefit to buffer oxidative damage [7,12]. γ-Amino butyric acid (GABA), the principal inhibitory synaptic transmission via neurotransmitter in the system of nerve tissue in vertebrates, comprising the brain and spinal cord, can incorporate excitatory inputs, coordinate neuronal processes, regulate synaptic plasticity, and halt the emergence and propagation of paroxysmal activity. It is rather remarkable that, in conjunction with KD, elevated levels of GABA have been seen, while the glutamatergic function has a significant drop trend in the hippocampus. Besides, all KD variations cause alterations in body-wide metabolism processes of energy, and in the end, the body fat rather than glucose is digested and converted to energy individuals need, increasing its reliance of KD in mitochondria for energy production, which makes ketone and KD result in high amounts of ATP synthesis [12]. Plus, notably in murine models, ketogenic diets can lead to a decrease in some autistic features, suggesting KDs as a promising treatment option for autism in spite of the limited number of observations while limited human research were examined for its positive efficacy on treating autism [7].

1.3.1.The reason why ketogenic diet has been used as an alternative option to treat ASD

In terms of ASD therapy for kids and teens, the primary treatments are educational and behavioral health therapies including high-intensive ABA therapy and early intensive behavioral intervention (EIBI), with medication serving as a crucial adjuvant [13,14]. However, not only a lack of effectiveness and licensed of pharmacological therapies to treat core symptoms of autism, but also young kids who suffer from ASD are more prone to drugs adverse consequences than those without this disorder, so that various therapies are required [14]. With people's preference for implementing a more "natural" approach and thought for a special diet to help reduce several problems about ASD, there is a leading to lend the impetus for using a dietary intervention to treat or at least mitigate symptoms of this neurological disorder.

2. Evident-based studies for KDs in treating comorbidities of autism

Several existing studies have illustrated that KDs have significant and efficient effects on treating ASD recently.

2.1. Anxiety, Depression, and ASD

Neuroendocrine system consists of nerve and grand cells which can make hormones, releasing them into the bloodstream to help promote mood stability and nutritional deficiencies may affect this system and worsen certain mental illness, for hormonal balance plays a vital part in regulating a physiological process, such as energy metabolism and stress management. In recent decades, there has been an emerging awareness of the connection between nutrition and depression [15]. Based on the studies' findings, it was discovered that dietary choices and nutritional content were linked to depression and anxiety. Major depressive illness subtypes may have an impact on body weight, body mass index and hunger, which increases the risk of other chronic diseases [16]. Children with ASD often struggle with anxiety, depression, and other mental health disorders. A study suggests that imbalanced GABA has linked to Children and teenagers with autism may experience overwhelm as confronted with daily demands, which may trigger anxiety of patients with autism and lead to anxiety symptoms, such as restlessness, tension, constant worry and fear, sleep problems, and fatigue. However, based on a study, presumed modulatory effects of KD on mood are also observed, suggesting KD seems to be a potential role as antidepressant to treat anxiety and depression [17].

2.2. Gastrointestinal Issues (GI)

According to prior research, neural control of the majority of GI physiology is accomplished through a vast network of enteric neurons and glia that span throughout the enteric nervous system (ENS) which is capable of controlling GI peristalsis and being affected by factors other than most central nervous system (CNS), while CNS illnesses have been linked to and even combined with changes in GI function and GI symptoms with psychological symptoms and psychiatric diagnoses [18]. As a result, alterations in the gut microbiota are connected to a wide range of illnesses including metabolic, neurodegenerative, and neuropsychiatric conditions like major depressive disorder and anxiety [19]. There is a belief that major depressive illness and gut bacteria interact in a bidirectional manner. It is hypothesized that there is a connection between the brain and the stomach, facilitated probably through the autonomic, enteric, and central nerve systems, as well as the gastrointestinal, immunological and neuroendocrine systems [20]. Recent studies suggest GI symptoms are strongly linked between gut and brain and even the severity of autism [7,21]. As a matter of fact, autism spectrum disorder is often accompanied by GI issues, which suggests ASD children are particularly prone to depression, physical discomfort, and externalizing issue than typical children and may affect behavior deficits, such as strained social communication, repetitive behavior and also lead to immune dysregulation [21,22]. Moreover, a study suggests chronic constipation in pediatric patients with autism might be a potential aspect of increased social impairments [23]. Limited studies showed that social and communication difficulties are associated with GI symptom severity while the notion that its severity has a close link between irritability, aggression and GI symptoms has been examined. Thus, gut mobilization can significantly improve behavioral symptoms in constipated children with ASD [22].

3. Treatments

3.1. Dietary interventions/Ketogenic diets

In ASD patients with GI symptoms, one study reveals that reduced transcriptions to host disaccharidases and hexose transporters mRNA, microbial dysbiosis in mucoepithelium and dysbiosis linked to host disaccharidase and hexose transporter mRNA expression, which was done by comparing intestinal biopsies from pediatric patients with GI illness and ASD to those with GI

disease alone as well as determining the expression of human genes involved in carbohydrate digestion and transport [21]. Indeed, reduced glucose transport and carbohydrate digestive ability can have far-reaching consequences, regardless of any underlying processes. For instance, malabsorbed carbohydrates can cause diarrhea, bloating or flatulence and exacerbate other gastrointestinal symptoms. The KD is a high-fat diet along with ultra-low amount of carbohydrates and an appropriate amount of protein, limiting carbohydrates and stimulating lipolysis to produce circulating ketone bodies. These ketone bodies are used as metabolites to replace glucose and generate energy for the brain, which is an effective strategy for alleviating the symptoms and comorbidities of autism that has gained increased attention in recent years [11,17]. Therefore, low carbohydrate diets (such as KD) are best for ASD patients.

As a proof of concept, KD can enhance social behavior and decrease autistic co-occurring conditions, such as attention deficit hyperactivity disorder (ADHD), obsessive actions, strongly attachment to observing the detail or motion of unusual objects, irregular sleep and even the occurrence of seizures etc., in people with ASD by stabilizing GABA, enhancing mitochondrial function, reducing inflammatory activity and oxidative stress in the brain, blocking the pathway of mTOR signaling and changing the intestinal flora [24]. Improvements in concentration, learning ability and social behavior are also observed after applying a ketogenic diet [7]. To date, parents and caregivers are inclined to choose dietary interventions, hoping to ameliorate their children's discomfort and assist them in coping with this disease [7].

3.2. Nutritional interventions/Probiotics and prebiotics

A study has shown a potential association with stunted gut microbiota in autistic kids may give rise to digestive issues (e.g., constipation or diarrhea) and cause discomfort (e.g., irritability and inability to concentrate). Moreover, some comorbid conditions of autism may account for malnutrition [7]. Thus, it is crucial to restore a healthy gut. Based on a study, implementing digestive enzymes and probiotics can help create a balanced environment for digestion so as to promote normal absorption. To enhance patients' nutritional status for preventing the onset of GI symptoms, a possible treatment involves the utility of prebiotics, probiotics or symbiotic, which can help lessen GI problems, alleviate autism-related behaviors, change microbiota composition, and improve inflammation [7]. What's more, the results of the literature review indicate that probiotics and prebiotics can improve mental health and psychological function (e.g., autism, anxiety, depression, and schizophrenia) and can be served as new medicines for autism.

3.3. Behavior therapies

ABA therapy and CBT therapy are two distinct methods that provide resources and strategies to address behavioral requirements of children and teens with ASD and can lead to remarkable outcomes for lessening symptoms of depression, anxiety, and social deficits [8].

3.3.1. ABA therapy

ABA therapy is highly-customizable to fit a broad range of autistic children's needs and their family, including improving language functions, cognitive and behavioral inflexibility, as well as social and self-care skills, integrating parents more into teaching sessions, and incorporating the special interests of each child [13]. Some studies indicate that a time-intensive ABA therapy from an earlier age can lead to a dramatic improvement in children with autism [25]. According to the study, ABA therapy is a type of highly data-driven approach using the science and learning of behavior to identify the most fitting behavioral interventions as well as a facility dedicated to attenuating certain behaviors, including communication, social skills, academics, along with fundamental competencies that are essential to success in school, chosen vocation and daily functions, involving fine and gross motor skills, personal hygiene, grooming, domestic capabilities, time management and job competence [25]. The data will be reviewed regularly by a board-certified behavioral analyst to see if the challenging behaviors (e.g., kicking, hitting, or self-injurious behaviors) are declining, if

adaptive behaviors are learned, and what skills need more support. What's more, ABA therapy lays stress on positive reinforcement as a means of increasing desirable behaviors and honing the skills of children, helping them gain independence and develop skills that they need [25]. Additionally, speech therapy (ST) can help autistic children address language and communication challenges. Occupational therapy (OT) can help support social engagement with autistic children. Physical therapy (PT) can help children experiencing developmental delay to strengthen gross motor skills. Those therapies are also used as multidisciplinary treatment options for alleviating autistic symptoms and optimizing the treating results [8]. Nevertheless, it should be highlighted that ABA is time-consuming owing to the fact that the best treatment outcomes require receiving the comprehensive, intensive sessions 25 to 40 hours per week. Furthermore, the time which it takes to see the result may differ from child to child.

3.3.2. Cognitive behavior therapy (CBT)

CBT, which is a particular assortment of psychological treatment that incorporates both cognitive therapy and behavioral therapy, focuses on how they relate between thoughts, feelings and behaviors. Based on evident-based studies, CBT shows positive effects on verbal children with autism and can be beneficial for kids and teens with both ASD, compulsive behavior as well as anxiety [26]. In accordance with studies, modified CBT is effective for various anxiety-related problems and compulsive behaviors associated with ASD, but it may require adaptions due to cognitive style differences, aiming to strengthen weaker regions while maximizing strengths curiosity and attention to detail. It can be seen that individuals who have been diagnosed with ASD, anxiety and avoidance behavior, CBT employing visualized language has a considerable shift in behavioral excess and avoidance behavior as well as cognitive surplus behaviors due to its incidence and degree [27].

4. Results and Discussion

Though there is a wide range of interventions available, a special consideration should be given to gain better knowledge about the most effective and evidenced-based interventions to provide proper clinical care.

4.1. Pros of Ketogenic diets

The positive impact of a ketogenic diet is now referred to as a potential dietary intervention [7,17]. In conclusion, KD has a good therapeutic effect on neurological diseases such as autism by regulating energy metabolism, neurotransmitters, anti-inflammatory, antioxidant and intestinal flora, enhancing mitochondrial function, exerting neuroprotective effects, significantly improving ASD patients' clinical symptoms and social behaviors and having broad development prospects.

4.2. Limitation

It is worth noting that the literature on human studies of KD's efficacy is sparse and presents relevant limitations. First, the effectiveness of KD in children with ASD remains inconsistent owing to diverse autistic symptoms and developmental differences presented by each of them. Second, attention should be paid to the possible ramifications of applying KD, including GI side effects, such as constipation or diarrhea, as well as potential risks, such as weight loss, fatigue, and nutritional deficiencies [7]. Third, eating problems in autistic children with reported values over 90 % undoubtedly reveals their lack of a balanced diet and an adequate nutrition intake [28]. In addition, multifaceted dimensions of food choice and atypical eating patterns including food refusal, eating only certain type of textures, meal irregularity can complicate the introduction of KD to ASD patients [28]. These nutritional problems are thought to derive from food intolerances and behavioral problems, oral motor disorders, and chewing problems [7,8]. Consequently, compared with healthy children, those with ASD fail to meet their nutritional requirements, adequately taking in recommended intakes of macronutrients and micronutrients. Last, it should be pointed out that food sensitivities can give rise to abdominal pain, puking, diarrhea, difficult and painful bowel movements,

and impairments in cognition and emotion, which can increase the severity of behavioral problems, adding challenges and difficulties to the implementation of ketogenic diet in patients with ASD and adherence to this dietary pattern [6,7]. Applying KDs can contribute to nutritional deficiencies so that continuous monitoring of children with ASD's dietary and nutritional health is also vital [7]. Moreover, some autistic children may have underlying medical conditions (constipation/diarrhea due to a gluten or lactose intolerance, or nuts allergy) and lead to nutrient deficiencies [7]. Accordingly, it is paramount to understand the root cause and address it first, and then work with a healthcare provider to see if supplementation may be beneficial. As common co-occurring conditions often affect the efficacy of multiple therapies and social supports for individuals with autism, the comprehensive assessment of this neurodevelopmental disorder and its comorbidities as well as personalized treatments are needed [8].

5. Conclusion

In a nutshell, some evident-based literature reviews point to the remedial effect of KD in managing ASD symptoms. However, whether this treatment is applicable to all patients with ASD has not been fully elucidated. All these studies, overall, suggest the effectiveness of this new approach is just for a short term, but not for treating chronically. Furthermore, to ensure the nutritional needs of children for growth and development are being met, there is need for the development of improved knowledge and more clinical research in this field for delivering relevant and effective health education and strategies to caregivers and clinicians to best treat this large population. After all, no single treatment is one-size-fits-all.

Authors Contribution

All the authors contributed equally and their names were listed in alphabetical order.

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