Review Article

Impact of Gluten and Casein Free Diet for Autism Spectrum Disorders: The Battle Continues

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ABSTRACT

Purpose of the review: The purpose of the evaluation is to inform society, "Autism Spectrum Disorders (ASD)" patients, well-wishers, and the parents of such patients about the advantages of gluten or casein-free diet as a therapeutic intervention for ASD by addressing all of their unresolved concerns. It focuses on the benefits, drawbacks, and clinical trials associated with the gluten-free and casein-free diet in controlling the pathogenesis of ASD, celiac illnesses as comorbid conditions in individuals with ASD, along with the relationship between celiac diseases, Human Leukocyte Antigen, and ASD.

Recent Findings: The population has recently become more aware of the benefits of a gluten-free and casein-free diet. Gluten and Casein, proteins found in foods like wheat and bread that are thought to bring in adverse symptoms in people with ASD, are not allowed in the diet. In some instances, it was clear that parents of such kids wanted to continue with the gluten-free or casein-free diet because they saw an improvement in their child's cognitive and behavioral functioning. However, society continues to debate the role played by casein and gluten in the pathogenesis of the condition and it is still not evident whether these diets can be considered a "godsend" for the treatment of ASD.

Summary: ASD is a subset of "neurodevelopmental disorders (NDD)" that have an impact on a child's ability to communicate and interact with others in social and communicative ways. Children with ASD are frequently observed to be confined to one location and shun social interaction. Therefore, these kids' parents and other loved ones must hunt for an effective treatment for these problems. Thus, this review focuses on the numerous outcomes of employing gluten-free and casein-free diets as therapeutic interventions against ASD, with a primary focus on their efficacy.

Keywords: Gluten-free diet, Autism, Casein-free diet, Human Leukocyte antigen, Celiac diseases.

INTRODUCTION

NDD has long been a source of concern for society not only because of the problems it causes but also because there aren't enough effective treatments and therapies for ASD and the symptoms it causes. NDD are primarily associated with abnormalities of the nervous system and brain[1-4]. This group of diseases is characterized by changes in motor, cognitive, communicative, and/or behavioral functioning during development. These conditions are encountered in infancy, childhood, and adolescence as a symptom of abnormal brain development and are clinically and etiologically heterogeneous. Since there are currently no effective treatments for ASD, researchers have been forced to look for alternatives, shifting their attention to the usage of a gluten-free diet (GUF) for the well-being of such individuals. Gluten and casein protein levels that are abnormal can lead to an increase in opioid activity in the central nervous system (CNS), which alters how it functions and eventually hurts people with ASD[5]. Further, a "leaky" gut, where opioids leak through the inflammatory and thinner gut lining in children with ASD, is thought to be how peptides with opioid properties produced from gluten and casein affect the CNS [6,7,8]. Therefore, it is evident and believed that these peptides exhibiting opioid activity are crucial in escalating autism symptoms in the CNS. Another matter that is of great concern is that patients with ASD have shown evidence of an imbalanced gut microbiota. The frequent incidence of gastrointestinal problems is therefore thought to be significantly influenced by this imbalance. Individuals with ASD have compromised blood-brain barriers and intestinal barriers. Toxins, pro-inflammatory cytokines, and partially digested peptides can all penetrate the blood-brain barrier and enter the CNS. The accumulation of these substances together exerts a negative impact on brain function [9]. Similar in molecular structure, the dietary proteins gluten (derived from wheat) and casein (derived from dairy products) are metabolized to form gluteomorphine and casomorphine, accordingly. It has been shown that these peptides can imitate the effects of opiates by binding and forming complexes with the opiate receptors of the CNS. It has been hypothesized that these opioid peptides produced during digestion cause the endogenous opioid system to become more active, which is associated with the symptoms of autism [10]. Therefore, a diet devoid of casein or gluten can aid in the treatment of ASD symptoms in patients.

Evidence suggests that over 80% of parents of children with ASD preferred a GUF and casein-free diet (CUF) for their kids and that 20% to 25% of these parents witnessed an improvement in their kids' ASD [11]. Additionally, individuals with ASD typically have higher levels of IgG in their bodies, and gluten can interact with IgG and cause major difficulties with metabolism [12]. Fig. 1 illustrates the various ASD symptoms and the impact of GFU and CFU on the improvement of these abnormalities.

In many innate as well as adaptive immunological responses, HLA genes on human chromosome 6 play a key role in its induction. In addition, autoimmune disorders along with immune system problems might be impacted by the HLA genes and their haplotypes [13]. It's interesting to note that studies have found frequent correlations between individuals with autism and HLA genes or haplotypes, which suggests that HLA genes have a role in the immune system's dysregulation [13-15]. Further, with the view addressing all open questions for the society and the widespread and broader use of both GUF as well as CUF to the ASD affected portions of this society, the review will focus on the differences between a normal child as well as an autistic child and then will further focus on the integrated relationship of ASD and celiac diseases with HLA.

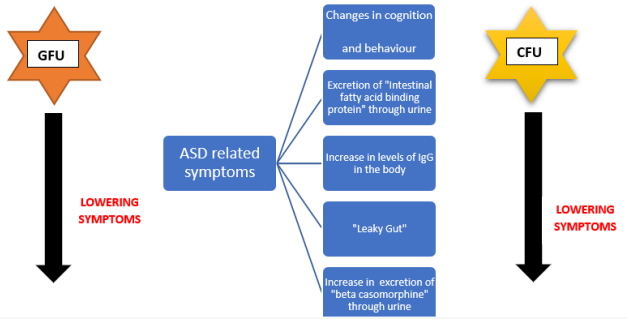

Figure 1: Effect of GFU and CFU on ASD associated symptoms

History of ASD

The pathophysiology of ASD has given rise to several theories, but more research is still required to fully comprehend it. The German psychiatrist Eugen Bleuler first used the term "autism" in 1911 to characterize a symptom of the most extreme forms of schizophrenia, a notion he had also developed. Psychiatrist Bleuler claimed that infantile desires to escape from disappointing realities and substitute them with delusions and hallucinations were the hallmarks of autistic thought. Even in Britain, the term "autism" was used by professionals in psychoanalysis, psychology, along psychiatry from the 1920s until the 1950s. In the 1940 Dr. Leo Kanner, identified and defined autism through his article in the year 1943 where he addressed youngsters who had delayed echolalia and how they want consistency in their lives. Additionally, he said that these kids had exceptional memory and were intelligently gifted [16,17]. As a result, Dr. Kanner came to understand autism as a neurodevelopmental impairment. In addition to this psychologists began using the term "autism" to refer to the antithesis of what it had previously indicated starting in the middle of the 1960s. In contrast to the extreme delusions and fantasies that were associated with autism in the 1950s, the term "autism" in the 1970s alluded to a complete absence of a subconscious symbolic existence [18]. For instance, when Dr, Michael Rutter, a UK-based renowned child psychiatrist asserted that "the autistic child has a shortage of fantasy rather than an excess", the definition of someone with autism was then fundamentally changed from "one who dreamed excessively to one who did not fantasize at all" [18].

Further, one six-year-old child out of the sixty-five children that were taken into consideration in the trial conducted by Goodwin and Goodwine (1969) had CED along with ASD [19]. This child showed significant improvements in his behavior relating to ASD following a GFU [19]. Another study by Goodwin et al., which is perhaps the first investigation into how gluten altered behavior in a group of youths with ASD, was published in 1971 [20]. For further comparison, a group of participants with schizophrenia and controls was also included. The participants in this study received either a cherry drink having gliadin as one of the constituents or sugar as a placebo added to it, along with the "sprue diet" (GFU), which they followed for one day. Following that, they were observed and evaluated using trans cephalic direct current electrophysiological recordings and blood count analysis. The investigation trial mentions some results, they mostly concentrate on the distinctions that seem to differentiate patients with ASD and schizophrenia, making only one statement on the effect of gliadin, which seems to lower plasma cortisol levels [20].

Further, a number of therapies have been developed for kids with ASD to assure their entire development and that they don't fall behind in the race as time has gone on and autism has come to be recognized as an NDD. For instance, in 1991, the federal government considered autism as a category that requires special attention with care. The term *"Asperger's syndrome"* was first included in the "Diagnostic and Statistical Manual of Mental Disorders" in 1994, extending the definition of ASD to include milder forms where people tend to be more physically fit, active as well as functional. The projected rate of autism increased to 1/110 children in 2009 from 1/150 children in 2007 [21]. Additionally, a number of ideas have been put out regarding the regulation of ASD. For instance, in the years 1998 and 2000, it was believed that the Measles, Rubella, and Mumps vaccines and "thimerosal," a substance found in vaccines, respectively, cause autism. However, additional research disproved all of these notions.

Distinguishing characteristics between a normal child and an ASD child

All of us are aware of how expensive therapy and counseling are for kids with ASD. We recognize that not all socioeconomic groups can afford such expensive medical care, which is why some kids receive no care at all. Through this review, the authors hope to improve the lives of the ASD community's underprivileged members and uplift their standard of living, by improving their cognitive ability as well as sociability skills.

There are noticeable and documented behavioral differences between a typical child and an ASD child. Lack of eye contact, poor social skills, repetitive behavior, poor cognitive function, shyness, problems with sensory integration, and frequent mood swings are typical early

signs of ASD in children [22,23]. Such actions could indicate that a child possesses ASD.

Correlation between ASD and celiac disease

ASD and CED are strongly correlated, according to several recent studies [24-28]. Gluten intolerance in those with a genetic predisposition associated with the Human Leukocyte Antigen DQ2/DQ8 homologs causes CED, a chronic autoimmune illness [29]. It has been discovered that CED directly affects the small intestine, causing persistent inflammation. Persistent enteropathic inflammation and "classic signs" of malabsorption, which include weight loss, recurrent diarrhea, abdominal distension, bloating, or pain, are the principal effects of CED on the small intestine, which is also the primary organ affected [30]. A clinical trial including 196 individuals was done to further support the theory that CED may contribute to the development of ASD [30]. The results showed an association between ASD and CED among the participants. According to the available published scientific literature, a rise in the protein Zonulin levels has previously been noted in children with ASD [31] (Fig. 2). Zonulin has also been linked to effects on the intestine's intracellular connections' structural integrity. Additionally, it has been emphasized that differences in blood-brain barrier function and intestinal permeability may play a role in the emergence of autoimmune diseases as well as NDD such as ASD [31]. Further by enrolling 25 patients with ASD and comparing them to 19 controls for probable Zonulin presence as determined by Enzyme Linked Immunosorbent Assay Techniques, the study further examined the relationship between ASD and CED. The study found that the 25 ASD patients had higher mean Zonulin levels than the other 19 patients who served as the control group (Mean Zonulin levels: 14.45 nG/dL) [31]. Thus, a significant change in the zonulin level was seen among the two groups taken for comparison.

Gluten, which digestive proteases partially break down, crosses the intestinal epithelial barrier. This partially broken down gluten interacts with the enterocytes, causing the production of IL-15, a vital interleukin that induces CED, releases zonulin, and activates tissue transglutamase.

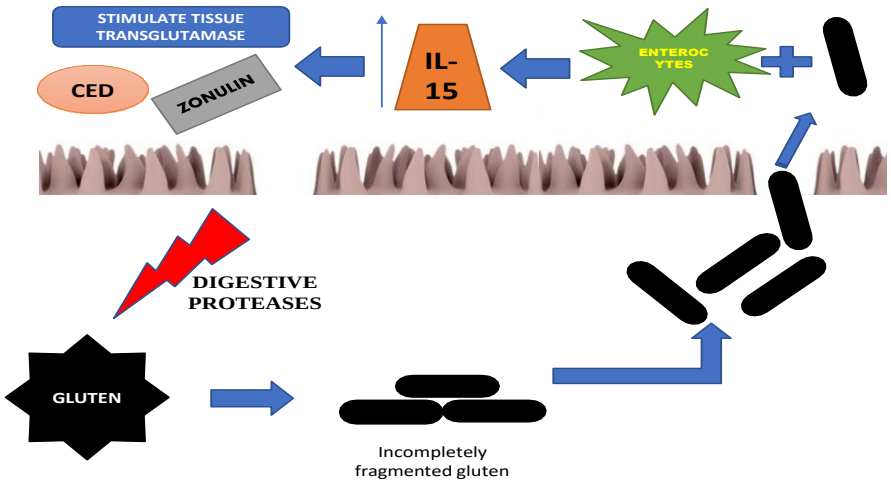

Figure 2: Effect of gluten on ASD and CED

Occurrence of amino acid at position 3 and 5 during the hydrolysis of Gliadinomorphine-7 , *bβ-casomorphin-7* along with *hβ-casomorphin-7*, inhibiting further degradation of these compounds

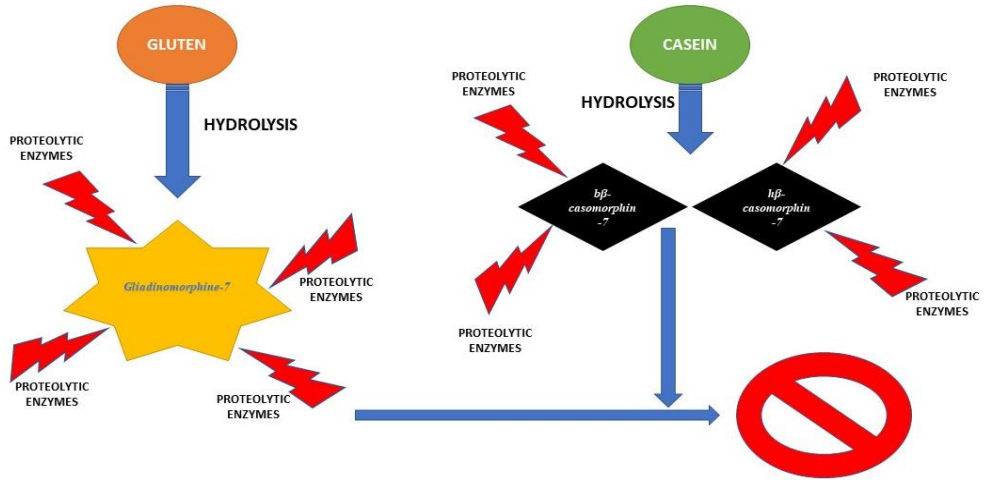

Figure 3: Hydrolysis of gluten and casein to produce "bβ-casomorphin-7" and "hβ-casomorphin-7" and "gliadinomorphine-7".

Additionally, a condition known as gut-microbiome dysbiosis is suspected to be comorbidity in ASD patients. As a result, it is hypothesized that casein and gluten may result in an even greater dysbiosis of the gut flora [32-35]. Al Dera et al investigations from 2021, which involved testing this theory on 35 young rats divided into seven groups, proved the idea. The third group rodent model of autism received treatment with propionic acid, while the other remaining three groups received treatment with clindamycin (CN) and propionic acid first, followed by a diet high in casein and gluten to test the relationship between gluten, casein, and dysbiosis as a comorbidity of ASD. The study presented several findings that imply a dysbiosis of the gut flora, sometimes known as a "leaky gut." In both CN-treated mice models that were given high-gluten and high-casein diets, elevated levels of Zonulin were found [34]. The ability of Zonulin to cause "leaky gut" can be inferred from the fact that it is recognized as a marker of the condition [36-38]. Casein and gluten are hydrolyzed to release the heptapeptides "*bβ-casomorphin-7*" and "*hβ-casomorphin-7*" and "*gliadinomorphine-7*". These proteins have distinctive conformations that are resistant to digestion by proteolytic enzymes of the intestine due to different amino acids occurring at positions 3-5 and the presence of a few proline residues [39-42] (Fig. 3).

Correlation between HLA genes and ASD

ASD is linked to both infections as well as autoimmune illnesses, and the genetic regulation of the human leukocyte antigen (HLA) pathway has a considerable impact on both of these conditions. To ascertain the relationship between ASD as well as HLA genetic diversity, additional study is required. When enterocytes are present, the important CED mediator interleukin IL-15 is produced. Additionally, tissue transglutaminase is stimulated and zonulin is produced [43,44]. The "HLA-E", "Major Histocompatibility Complex - I chain related protein A," and their associated receptors on the enterocytes are claimed to be upregulated by IL-15. Additionally, "cluster of differentiation 94 (CD94)" and "natural killer group 2D (NKG2D)" are believed to be upregulated as a result of it as well. Thus, they cooperate and work as a unit to moderate the intestine's mucosal layer damage [44,45].

In the study by Bennabi et al. (2018) [13], 350 individuals without ASD and 474 persons with ASD had their genotypes and HLA-II DQB1 and HLA-II DRB1 haplotypes analyzed. According to the study, the protective HLA haplotype "HLA-DRB **17-DQB1** 02" was more prevalent among the group of healthy individuals, whereas "HLA-DRB1 **11-DQB1** 07" was more prevalent among the individuals with autism spectrum disorders [13]. The connection between HLA, celiac disorders, and finally ASD has been made evident by this study. Additionally, it is understandable why people with ASD disorders frequently experience gastrointestinal illnesses like diarrhea, bloating, or abdominal pain [14]. This study has established a link between HLA, celiac disea ses, and finally ASD. As a result, HLA plays a role in the pathophysiology of ASD and is pertinent to both the gastrointestinal system and the disruption of gut-brain synchronization.

A further case-control research by Tamouza et al. in 2019 [15] examined 131 ASD individuals, 33 of them had regressive autism (REA) and the remaining 98 had non-regressive autism (NRA) to determine the role performed by HLA in ASD. The study discovered that persons NRA (62/98) were more likely to have the HLA haplotype "HLA-DPA1 **01-DPB1** 04" than those with REA (16/33). Further analysis revealed that this HLA haplotype was more prevalent in healthy people taken as controls than in people with autoimmune diseases (non-psychiatric). It can be said that having this specific haplotype acts as protection against REA because its presence has been detected more frequently in people with NRA as well as in healthy subjects (people devoid of ASD) [15]. As a result, the review has found a significant correlation between HLA haplotypes and ASD.

Composition of GUF and CUF [6,8]

GUF and CUF differ from normal foods in lacking the presence of proteins, gluten, and casein respectively. Gluten is found most easily in wheat-derived products whereas casein is referred to as a milk protein which as the name suggests is obtained from dairy sources. Foods and drinks made from wheat, rye, and barley contain a significant amount of the protein called gluten. Oats are generally considered to be naturally gluten-free, however, their inclusion in GUF is still debatable. Foods and drinks made from wheat, rye, and barley contain a significant amount of the protein called gluten. Oats are generally considered to be naturally gluten-free, however, their inclusion in GUF is still debatable. Hence, the consumption of such foods should be avoided for ASD-affected patients. The nutrition of such patients by avoiding such nutrient-dense foods may raise a concern in the readers' minds. Therefore, these patients should consume foods that are readily available and fall under the category of gluten-free foods. In addition to fresh produce, people with ASD disorders can also eat fish, meat, poultry, eggs, nuts, beans, and legumes because they are gluten-free. In place of wheat, people can consume buckwheat, arrowroot, millet, rice, cornmeal, etc. as they are said to be gluten-free. Today, its effectiveness in the intervention of ASD sufferers has spread to most of the spheres of society. Additionally, patients with celiac disease (CED) are also suggested to consume such diets [6,7,12]. Recent research has shown that CED has a frequent correlation with ASD in patients [24-26]. However, this association has not been supported by numerous additional investigations.

In addition to GUF, patients with ASD are advised to move away from consuming casein, a protein found in milk, and toward consuming CUF. Therefore, for their greater well-being, such individuals should always refrain from consuming milk products [8]. However, almond milk, soy milk along with rice milk, all can be consumed as they are considered to be grouped under the category of CUF.

The fact that foods like whole wheat bread or flour or milk products include several critical minerals including calcium, iron, riboflavin, niacin, folate, as well as fiber, presents a significant challenge for those who avoid gluten and follow a GUF or CUF. To live a healthy life, all of these are necessary for an individual's metabolic system to work properly [6]. However, today several alternatives to enrich the nutritional values are available for patients with ASD consuming GUF OR CUF. For instance, several artificial vitamins and mineral supplements are available, upon prescribing by a qualified medical professional. Also, mineral-enriched food products such as calcium-fortified orange juice, soy milk, or rice milk can be used to keep their nutritional requirements intact for proper metabolic functioning along with following a GUF or CUF.

The composition of GUF and CUF as well as methods for ensuring optimal nutritional balance in ASD patients who choose GUF and CUF are therefore successfully emphasized in this review. To assist those in the ASD community who are considering choosing GUF or CUF, the review will go on to discuss both the benefits and drawbacks of GUF and CUF for the readers.

Benefits of GUF and CUF

1. Using GUF or CUF helps avoid the induction of gastrointestinal and its associated difficulties because people with ASD can also exhibit signs of digestive issues.
2. Patients with ASD opting for GUF or CUF have addressed an improvement in their sociability and cognitive skills [26].
3. GUF typically consists of low-cholesterol foods, which increases the levels of High-Density Lipoprotein (HDL) and decreases the levels of Low-Density Lipoproteins (LDL) [12].

Drawbacks of GUF and CUF

1. Inadequate dietary intake via GUF and CUF.
2. The high cost of GUF and CUF acts as a barrier for impoverished groups of society to opt for them.
3. Heightened danger of obesity [46].
4. Affected the body's regular metabolism of lipids and carbohydrates [46].
5. Lack of fiber in GUF and CUF can also impact how these foods are digested [12].

The review has explained to its readers the components of GUF and CUF as well as their advantages and disadvantages. The review will also list and search for various clinical trials under the published scientific literature accessible to examine the efficacy of GUF and CUF in the treatment of ASD.

Table 1: Clinical Trials to study the efficacy of GUF and CUF on ASD

Test group	Diet of control group	Diet of test group	Duration of trial	Results	Reference
ASD impacted children grouped between the ages of 4 and 7	GUF, CUF, and consuming brown rice flour each day (1g/kg) to 6 childrens	GUF, CUF, and consuming gluten powder and non-fat dried milk (both 0.5g/kg)	1 month	Very little (No significant changes) was seen in either group's levels of behavioral hyperactivity, irritability, inattention, or Lactulose/Mannitol ratio. (Based on CPRSR, ABC, CBCL)	47
ASD impacted children grouped between the ages of 2 and 16	Regular dietary intake for seven childrens	GFU and CFU to seven childrens	3 months (Crossover after every 6 weeks)	Very few (No significant) behavioral changes or changes in peptide levels in urine samples were noticed; however, one teacher noticed that the language of two children had improved, and parents of seven children had noticed that their child's language had improved and that their child's hyperactivity had decreased. The parents of the other nine children chose to keep their child on GFU and CFU. (Based on CARS, ADIR and ECOS)	48
ASD impacted children grouped between the ages of 4 and 10	Regular dietary intake for 34 childrens	GFU and CFU to 38 childrens	Stage 1: 8 months Stage 2: next 12 months Stage 3: next 24 months.	Reduction in test scores of ADOS, GARS, and ADHD-IV- Improvement in child's condition. An improvement in developmental behaviors can be seen in an increase in VABS test scores. (Based on GARS, ADOS as well as VABS)	49
ASD impacted children grouped between the ages of 4 and 7 along with	GFU and CFU in addition to six biscuits containing 30 g of rice meal daily	GFU and CFU in addition to six biscuits containing 11 g of gluten and 12g of casein daily	1 week	There were no discernible behavioral or cognitive differences between the two groups, nor were there any differences in the amount of IFABP that was excreted in the urine. (Based on AWPS, PDDBI, IFABP Excretion via urine)	50

symptoms of maladaptive behavior, excretion of IFABP through urine	supplement to 36 childrens	supplement to 38 childrens			
ASD impacted children grouped between the ages of 3 and 5	Regular dietary intake for fourteen childrens	GFU and CFU diet intake by eight childrens.	12 weeks	No significant behavioural changes between the two groups observed. (Based on CBCL Scores)	51
Thirty-seven ASD impacted childrens grouped between the ages of 2 and 18	Regular dietary intake for twenty patients	GFU and CFU diet intake by seventeen patients.	12 months (Crossover after 6 months)	No significant behavioural changes between the two groups observed along with no significant decrease in "beta-casomorphine" concentration in urine.	52

ADOS: Autism Diagnostic Observation Schedule; ADHD-IV: Attentional Deficit Hyperactivity Disorder; GARS: Gilliam Autism Rating Scale; IFABP: Intestinal Fatty Acid Binding Protein

DISCUSSION

With the development of science today and the need to find a dietary intervention to treat ASD, researchers from all over the world have developed a variety of clinical trials to evaluate the efficacy. No distinct or clinically meaningful improvements have been noted in the effectiveness of GUF and CUF as a dietary supplement therapy intervention for ASD disorders in childrens aged between 2 years and 18 years among the several clinical trials reported in Table 1. However, it has been demonstrated in the past that ASD issues affect a child's metabolism in a variety of ways, including an increase in IgG count, an increase in "beta casomorphin" in the urine, the excretion of IFABP via urine, and behavioral and cognitive alterations [12,49,53]. Focusing on these clinical trials, it is still up for debate in society whether dietary interventions like GFU or CFU have any proper significance in the intervention of ASD. The clinical trials failed to bring significant and proper improvement in the condition of childrens. Still, contrarily it was observed that in the trial conducted by Elder et al. in 2006 48, teachers and parents reported an improvement in the child's cognitive and sociability behavior in their children's. In contrast, parents of several children's even decided to opt for GUF and CUF further for their children's [48]. The basic symptoms of autism spectrum disorder, as assessed by established scales, did not change statistically significantly between groups, with a few minor exceptions for some subgroups. Additionally, because no data on specific patients were supplied, it is impossible to reliably determine the clinical significance of the results. Also, it is conceivable that the impacts anticipated from dietary modifications are modest and take longer than a year or more to notice.

The valid association between ASD and related CED symptoms, on the other hand, has also been demonstrated in scholarly literature. Today, it has been established that autistic patients exhibit all of the related symptoms of CED, including gut flora dysbiosis and an increase in zonulin levels. In light of this, the impact of gluten and casein combined goes beyond ASD to include CED. Additionally, gluten is only partially broken down by digestive proteases, allowing it to pass through the intestinal epithelial barrier[54,55]. When this incompletely fragmented gluten interacts with the enterocytes, it triggers the synthesis of IL-15, a crucial interleukin that helps to induce CED, release zonulin, and stimulate tissue transglutaminase [43,44,56] (Fig. 2). The interleukin IL-15 stimulates the release of the enterocytes' "HLA-E", or "Major Histocompatibility Complex-I chain-related protein A", and its associated receptors. HLA and ASD are closely related to one another. Numerous studies have shown that patients with ASD have certain HLA haplotypes, and these patients also go on to develop CED as ASD-related comorbidities. For the benefit of those with ASD, avoiding gluten is advised because it can cross the intestinal epithelial barrier and contribute to the production of interleukins and HLA. Casein and gluten exacerbate both ASD and CED given that they are believed to be linked to both disorders [33,34].

Future aspects

1. The review makes it clear to its audience that short-term clinical trials are not relevant for comprehending the function of GUF and CUF as a treatment options for ASD. It is important to carry out large-scale double-blinded clinical trials for a longer period to better understand the impact of these dietary therapies and to establish GFU and CFU as validated interventions for ASD [57-61].
2. Future longitudinal investigations may also focus on the relationship between the microbiome, the gut along with the brain, which may be a mechanism underlying the emergence of neurodevelopmental disorders, as well as the symptom-relieving effects of elimination diets.
3. Children participating in trials should be informed of the GUF and CUF's nutritional imbalance, along with their parents, and alternative research should concentrate on maintaining the children's nutritional balance through the use of artificially safe

supplements or restricted diets that include infused minerals and vitamins for a healthy metabolism.

CONCLUSION

About the use of GFU and CFU, numerous research has reported a variety of findings, but none of them have offered a conclusive opinion. It should be emphasized that all of the experiments used to evaluate the effectiveness of GFU and CFU were carried out for very brief periods. To further serve the needs of this society and the poor segment of this society, the authors have highlighted all the distinctive traits of an autistic child in this review. It is still unclear whether GFU and CFU can improve the health of the ASD community by restraining the pathophysiology of the condition when it comes to the recommended CFU or GFU diet for people with ASD. However, these diets have been clinically examined, and no instances of GFU or CFU having disastrous effects on children who followed them have been documented based on the existing published literature. Therefore, such diets should only be adopted by people after careful consideration of the advantages and disadvantages for the patients and their families. Additionally, it must constantly be remembered that GFU and CFU lack several key nutrients, making it impossible to refer to them as a balanced diet. Therefore, before a patient chooses to follow a diet, medical practitioners should strictly prescribe appropriate and safe vitamins and other key nutrient supplements. Thus, despite significant advances in technology along with science, the effectiveness of these diets for ASD is still up for debate. As a result, further thorough research is advised to find the best treatment option for our society's ASD community so that they won't continue to be treated unfairly and fall behind in the race against time.

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