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Review

Gluten and Casein: Their Roles in Psychiatric Disorders

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ABSTRACT

Gluten is a herbal protein found in grains such as wheat, rye, and barley. Casein is an animal protein found in cows, goats, sheep, and human milk. Since it is not digested properly in people suffering from intestinal-based psychological disorders, its chemical properties turn into structures similar to morphine. Gluten and casein peptides such as gluteomorphin and casomorphine were found in urine samples taken from patients with diseases like Down syndrome, schizophrenia, depression, autism, and epilepsy. These peptides cross the vascular structure through the blood to the brain and the fluid in the brain, causing the function of some areas of the brain to be slowed down. This condition, which originates in the digestive system, is more frequent in people who have an intestine-based psychiatric disease. The psychiatric effects of gluten and casein on different individuals were examined in this review based on the research in the literature, and it was revealed that the findings of these effects were not the same in everyone. Although a gluten-free, casein-free diet is not a cure-all, it can help lessen psychological symptoms.

Keywords: autism, casein, depression, gluten, gluten-casein diet, schizophrenia

With each food consumed, the body converts nutrients into various digestive products, which give different results for each individual via a mechanism that differs from person to person. Due to increased intestinal permeability, various diseases and the effects of converted digestive products left in the body can affect the brain, causing an increase in the symptoms of the disease. Gluten is a vegetable protein, but it can lead to various health problems. They can be divided into three types: autoimmune, allergic, and non-allergic. Autoimmune diseases can be called celiac disease (CD), dermatitis herpetiformis (DH), and gluten ataxia (GA). Wheat allergy (WA) is an example of an allergic health problem. Non-celiac gluten sensitivity, neurological disorders, depression, migraine, autism spectrum disorder (ASD), and obesity can be given as examples of autoimmune or non-allergic health problems.[1,2]

Casein is an animal protein that has the same mechanism of action as gluten and can also trigger some psychiatric disorders' symptoms. Most people turn to the gluten-free/casein-free (GFCF) diet to reduce symptoms and contribute to the improvement of the disease. Although exact findings were not obtained in every individual as a consequence of the trial, many people noticed that the symptoms diminished as a result of the diets created.[3]

GLUTEN

Gluten, the primary storage protein of wheat grains, is a complex combination of hundreds of distinct proteins. Secalin in rye and avenin in barley and oats are both storage proteins that are referred to as "gluten." Gluten protein networks vary due to different components and sizes, as well as variability caused by genotype, growth conditions, and technological processes. Gluten is heat-resistant, can act as a binding and expanding agent, and is used as an additive for better texture, moisture retention, and flavor in processed foods.[4] Gliadin comprises peptide sequences that are extremely resistant to proteolytic digestion in the gastrointestinal system, including

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gastric, pancreatic, and intestinal proteolysis.[5] Gluten consumption in a Western diet is estimated to be 5-20 g per day, and it has been linked to a variety of health problems.[6] Gluten-containing cereals (wheat, rye, barley, and oats) are essential staple foods. Gluten is one of the most complex protein networks and is crucial in controlling dough rheological qualities.

The content of a wheat germ consists of moisture, protein, starch, lipids, and ash. Its protein composition is separated into two categories: gluten and albumin. When the subcomponents of gluten are examined, the structures of semi-gliadin and semi-gluten are revealed.[4] Since the processing properties of wheat flour are affected by such factors as flexibility and stickiness, gluten has a significant impact on the production of foods such as baked goods, pasta, and noodles.[7] The amino acid cysteine is extremely important for the structure and functionality of gluten. Most cysteines exist in an oxidized state and form intrachain disulfide bonds within a protein or interchain disulfide bonds between proteins. These bonds are the main target of most redox reactions that occur during seed ripening, grinding, dough preparation, and baking.[8]

Disulfide bonds play an important role in determining the structure and properties of wheat gluten proteins. Comparison of the sequences of monomeric gliadins and polymeric glutenin subunits allows the identification of conserved and variable cysteine residues.[9] The peptide chains contained in gliadin are highly resistant to gastric, pancreatic, and intestinal digestion, and these chains leave the digestive system intact. This difficult digestion is due to the high content of gliadin amino acids, proline, and glutamine. This proline-rich structure forms tight and compact structures that cause adverse reactions in celiac disease.[10] Amylase trypsin inhibitors (ATI) make up about 2-4% of the total protein in modern wheat. ATIs are albumin proteins involved in the plant defense mechanism and have recently played a role in gluten sensitivity.[11] It is a carbohydrate-binding protein found in the wheat kernel. Its combination with gluten consumption can induce both intestinal and extra-intestinal symptoms because it causes epithelial damage and weakens immunity.[12] Gluten-related health problems also include autoimmune or non-allergic problems. A few of these are diseases such as non-celiac gluten intolerance (GI), neurological disorders, depression, migraine, autism, and obesity.[4,13] When the relationship between schizophrenia and gluten was investigated, different findings were obtained according to individuals. Schizophrenia is a chronic disease and has various clinical manifestations. The onset form shows different features according to the symptoms and the course of the disease, and it is also known to be genetic. Although its incidence is 1%, it can cause serious illnesses, so it is very important to develop an effective treatment method.[14] According to the hypotheses obtained in some studies, reductions in schizophrenia were observed when they removed gluten from their diet. Epidemiological studies have revealed that the incidence of celiac disease in patients with schizophrenia is almost twice that of the general population, which raises the question of whether gluten causes schizophrenia. Although various studies have shown that when gluten is removed from the diets of schizophrenia patients, there is a decrease in schizophrenia symptoms, different studies have shown otherwise.[15] The intestinal brain connection plays a very important role in restoring the internal balance of our body. Any dysfunctional behavior in this system is related to psychiatric diseases, as well as non-psychiatric diseases. The terms microbiome and microbiota are used to describe all microorganisms that live in populations of microorganisms in different ecosystems of the body of all microorganisms.[16] As the most common types of bacteria, bacteroids, actin bacteria, and proteobacteria can be given as examples. The physiological primary role of the microbiota is to strengthen the metabolic and immune systems and provide intestinal motility. Thus, the microbiota protects the host from infections, assists in food digestion, aids in medicine absorption, and contributes to fat absorption and breakdown.[17]

Environmental factors such as inflammation, infection, and stress affect epithelial integrity and endothelial barrier structures. Studies have shown that diseases such as intestinal-based celiac disease, schizophrenia, migraine, and autism have established a deep connection between autoimmune disorders. According to some biological variables influencing the disease, secretory immunity to dietary antigens, intestinal inflammation, exposure to *Toxoplasma gondii* parasite, endothelial barrier abnormalities, and microbial dysbiosis can cause systemic immune dysregulation in the gut-based process.[18,19] In schizophrenic patients, bacterial translocation and intestinal inflammation markers have shown that there is structural damage to the intestinal system barrier of the patient, and because of this damage, the composition of the intestinal microbiota may be affected. A gluten-free, casein-free diet program to be applied to patients with schizophrenia may reduce the symptoms of this disease.[20] *Toxoplasma*

gondii translocation is usually seen as a result of this intestinal damage, and it is thought that protozoan infections will increase the symptoms of schizophrenia.[21] High concentrations of *T. gondii* are found in patients with disease-onset schizophrenia.[22] Schizophrenia is a disease associated with many areas of the brain and neurons, and glia can adversely affect them. Highly neurotrophic protozoan *T. gondii* hosts and affects various cells of the brain, such as microglial cells in the cerebellum, neurons, astrocytes, and Purkinje cells. Additionally, *T. gondii* is thought to cause symptoms of schizophrenia by its effect on dopamine and gamma-aminobutyric acid neurotransmitters in areas of the brain associated with schizophrenia.[23] Inflammation of the gastrointestinal tract with *T. gondii* leads to increased levels of inflammation and increased absorption of antigens from the intestinal tract.[24]

The relationship between food antigens and the Toxoplasma parasite is thought to be dependent on the gastrointestinal tract.[25] An increase in the levels of anti-gluten antibodies over time was observed in mice infected with *T. gondii* by the intraperitoneal, peroral, and prenatal vaccination routes compared to mock-infected mice. Higher anti-gluten IgG levels of peroral infected females than males indicated that gastrointestinal infection by *T. gondii* elicited a significant anti-gluten immune response in a sex-dependent manner. Similarly, it was found that in mice, seropositivity through peroral administration of *T. gondii* was significantly higher than seronegative. The offspring of *T. gondii* seropositive mice showed significantly higher levels of anti-gluten IgG antibodies compared to the offspring of uninfected mice. It has been understood that there is a direct relationship between *T. gondii* infection and the production of antibodies against gluten.[26] In a study, anti-*Saccharomyces cerevisiae* antibody (ASCA) was measured as a marker of inflammatory bowel disease, ASCA levels were found to be higher in schizophrenic patients and patients with schizophrenia onset compared to a healthy control group. Moreover, ASCA levels showed a linear relationship with anti-gluten IgG levels in patients with incipient schizophrenia and with anti-gluten IgG and anti-casein IgG levels in patients with schizophrenia. In a group of patients with a recent onset of schizophrenia and bipolar disorder, a significant correlation was found between *T. gondii* IgG, anti-casein IgG, and anti-gluten IgG levels.[27] In a study conducted on American military personnel, although there was no relationship between schizophrenia, gliadin, and *T. gondii*, antibody levels to casein and the risk of schizophrenia were found to be at the limit of significance.[28] Another view of the increase in gluten sensitivity is opioid peptides derived from exogenous protein, such as milk or plant, which are referred to as "exorphins".[29] Gliadin exorphins A5, A4, B5, B4, and beta-casomorphine-7 are commonly used exorphines.[30] An increased concentration of beta-casomorphin-7 in the blood can intensify the symptoms of autism, schizophrenia, and allergy, known as an apparent life-threatening event (ALTE).[31] It also has the effect that beta-casemorphine increases the release of histamine.[32] Morphine has the same effect as endorphins and has an extreme opioid effect, they act by binding to opioid receptors in the central nervous system (CNS) and gastrointestinal tract. This causes both desired and undesired effects. If examined in detail, they reach the CNS through the blood-brain barrier (BBB) by the trans-cellular passage from the intestines of the person to the blood or lymphatic circulation, through receptor-mediated endocytosis.[33] They bind to opioid receptors in the central nervous system and induce schizophrenia-like behaviors. They cause dopaminergic and possibly cholinergic changes in neurotransmitter levels in the brain.[34,35] Neuroactive small peptides with opioid-like properties were found in high concentrations in urine samples from schizophrenia patients.[36] The gastrointestinal inflammation marker level and ASCA were significantly increased in schizophrenia and autism patients. In an experiment with a control group, a significant correlation was found between increased ASCA levels and anti-casein, anti-gluten IgG antibodies.[15]

Various results have been obtained according to the data in the gluten-free diet study applied to schizophrenia patients. Dohan et al.[37] conducted controlled studies to support the hypothesis that "cereals may be the pathogenesis of schizophrenia". A gluten-free, dairy-free diet was applied to 47 male schizophrenic patients, a high-grain diet program was applied to 55 male schizophrenia patients, and as a result, patients who were given a gluten-free diet were discharged twice as fast as the other group. Similar results were observed in the studies of Rice et al.[38] While an increase in psychiatric symptoms was observed in only one patient in the gluten-fed group, improvement was observed in two patients on gluten-free and dairy-free diets. One of these patients was discharged after 13 years. Vlissides et al.[39] applied a gluten/gluten-free diet to 24 patients with chronic schizophrenia in their 14-week study. The behavior of the patients was evaluated with other inpatient profiles. In the gluten-free diet group, improvements

were seen in five of the twelve measurements. Psychiatric symptoms recurred again in patients who experienced significant improvements when gluten was re-added to their diet. Potkin et al.[40] followed a gluten-free and dairy-free diet for 13 weeks for eight chronic schizophrenia patients. Each patient was subjected to a 30 g gluten diet or received a placebo for at least five weeks. They found no significant difference at the end of the study. Some studies have produced conflicting results.

Although the authors noted that most people with schizophrenia would not benefit significantly from eliminating gluten from their diets, it also turned out that patients who eliminated gluten from their diets had the opposite benefit. Therefore, in many studies, the relationship between schizophrenia and celiac disease, and the mechanisms of the common ground between these two diseases are still unknown.[41] Recent research shows that these two diseases share similar genetic regions related to gluten. Results of immunological studies revealed that the anti-gliadin immune response in schizophrenia has antigenic specificity different from that of celiac disease. Although most schizophrenic patients with increased anti-gliadin antibodies do not have celiac disease, the presence of increased antibodies to gluten is common to the immunological abnormalities found in both diseases.[42] Today, celiac disease and gluten sensitivity can easily be detected with the finger-stick method or serological tests.[43] If gluten sensitivity is the cause of symptoms in people with schizophrenia, performing a simple test and following a gluten-free diet may help relieve some symptoms. A gluten-free diet can also increase efficacy in antipsychotic therapy.[15]

CASEIN

Casein is a complete protein that includes all of the essential amino acids that our bodies require to operate. Casein is a tasteless white substance. Casein is produced by all animals as a component in milk for their offspring. Human milk includes 40% casein and 60% whey protein, but cow's milk contains 80% casein and 20% whey protein.[44] Since casein binds to calcium and phosphorus, milk is a good source of these vital minerals.

Although the previously mentioned whey protein and casein may seem to be the same, they are different substances. Whey and casein are animal proteins derived from milk. Whey protein enters the blood within an hour, while casein protein takes 7-8 hours to enter the blood. Cow's milk contains more casein than breast milk. Casein is more difficult to digest than whey which has a much higher nutritional value. As a protein supplement, casein provides all the amino acids necessary to improve our workouts and put our strength on a solid foundation. After a hard workout, it repairs the small tears that form in the muscle fibers, making them bigger and stronger. Proper sleep and adequate protein intake are crucial for muscle recovery. Casein products work by providing an extra protein boost to support muscle tissue.[45]

As a structure and property, casein is found in nature in a liquid surrounding the molecule. This structure is called "mycelium". The micelle can be thought of as a solid little balloon mixed into a solution. There are four subtypes of casein: αS1-casein, αS2-casein, β-casein, k-casein. Except for k-casein, the others are calcium sensitive.[46]

Calcium-sensitive subspecies bind calcium and phosphorus, transporting these minerals throughout the body for digestion and absorption. K-casein serves a structural function in the micelle, keeping it intact until digestive enzymes remove it. After k-casein is metabolized, the micelle turns into an insoluble mass. This first step of digestion converts casein into a form that is more resistant to degradation. Casein is considered a slow-digesting protein, as several steps are required for the disassembly of the micelles.[47] Like every protein, casein is a substance that should be taken into the body due to its benefits. Drinking a casein protein-based beverage during regular workouts in adults can contribute to muscle and bone health. One cup of milk contains about 300 mg of calcium found in casein micelles. The amount of calcium required for most adults is 1000-1200 mg daily.[48] Considering the importance of adequate calcium and protein intake for bone health, foods containing casein may help prevent osteoporosis. As mentioned earlier, casein is used by bodybuilders as it is digested slowly. While soy protein and whey protein are rapidly released into the bloodstream, casein takes about 6-7 hours to digest.[45] The reduced digestion rate of casein continuously delivers amino acids to damaged muscle tissue over a long period of time after a workout, accelerating recovery. Slow digestion contributes to satiety. It helps to feel full for a long time and reduces unhealthy food cravings. Although caseins are proteins that must be taken into the body, they can turn into harmful substances in some people. A component of casein known as casomorphins acts like opiates as they break down. Casein is digested slowly, while casomorphins bind to opiate receptors in the brain and can cause one to

become addicted to dairy products.[49] While many people think that their negative reaction to dairy products is due to lactose intolerance, it may be casein because casein is broken down very slowly, and it puts a great strain on the digestive system. Digestive difficulties may be due to the lack of enzymes necessary to digest such proteins from the intestines.[50]

Casein is used as a strong adhesive in wood bonding. Due to its thick and coarse properties, it is used as a casein adhesive for long-lasting effects of durability. Casein can block the human respiratory system. Wheezing, coughing, congestion, runny nose, and itching in the eyes may be caused by casein.[51] Casein has a very similar molecular structure to gluten, and often people with gluten intolerance can also experience casein intolerance, too. According to research, there is a 100% correlation between gluten and casein intolerance.[52]

The mechanism of action of casein and the symptoms of schizophrenia are not known for certain, but caseins contain casomorphin formations. Casemorphins are casein-derived neuroactive peptides that can alter brain development. In the urine samples of patients with schizophrenia, casomorphine levels were increased. In addition, cow's milk consumption with the casein A2 genetic variant, which is less capable of producing casomorphine, was associated with less severe schizophrenia symptoms on a population basis. However, most of these studies have been conducted with small populations and inadequate controls, and have not been replicated or studied in depth in other populations. As a result, a nonlinear relationship was determined between schizophrenia and IgG levels.[53]

Inflammations and other immune processes are associated with some psychiatric diseases. Although antigenic triggers specific to bipolar disorder have not yet been identified, testing whether bovine milk casein is associated with bipolar disorder and whether the experimental groups recognize different casein protein epitopes than the control groups revealed that individuals with bipolar disorder had high anti-casein IgG. Unlike the control groups, it was seen that the serum of individuals with bipolar disorder did not inhibit the binding of casein-reactive animal serum. Based on the data obtained, the relationship between anti-casein IgG and bipolar diagnoses, history of psychotic symptoms, and bipolar phase severity suggests that psychosis and bipolar phase components of casein-induced immune activation may be related. Case-control differences in epitope recognition include changes in how the casein molecule is digested, and how casein-derived constructs are immunized.[54]

Autism was covered in the autoimmune or non-allergic gluten sensitivity section. Autism spectrum disorders (ASDs) are a group of neurodevelopmental disorders with deficits in two main areas. ASD is usually diagnosed in childhood. Although it affects people of all ages, autism is mostly seen in children in this context.[55,56] It is three times more common in boys than girls and is a lifelong condition.[57] Individuals with autism have difficulty in social interaction and communication and exhibit repetitive or restrictive behaviors. ASD is often associated with comorbidities such as intellectual disability and anxiety. Although the exact cause of ASD is not known, prenatal damage, genetic, environmental, and immunological factors also play a role. Among the most common medical diseases associated with autism include mitochondrial dysfunction disorder, impaired transmethylation, and transsulfuration pathway, oxidative stress, immunological dysfunction, and gastrointestinal abnormalities.[58] In addition, the severity of gastrointestinal symptoms correlates with the severity of autism symptoms.[3,59] Chronic constipation ranges from diarrhea to irritable and inflammatory bowel issues. Although studies concluding that children with autism have food allergies in the gluten and casein relationship of autism are limited, 36 children with autism were evaluated.[60] In addition to IgE levels, serum IgG, IgA, and IgM-specific antibody levels for cow's milk and egg proteins were evaluated using the scratch test in patients with autism. Increased IgE levels were noted in 33% of children with autism. Another study evaluated 35 participants with autism and 21 siblings of participants with autism. Statistically high plasma concentrations of IgA antibodies to alpha-lactalbumin, beta-lactoglobulin, casein, and gliadin have been found in children with autistic disorders. Plasma concentrations of alpha-lactalbumin, alpha-lactoglobulin, and IgG antibodies to casein were significantly higher in participants with autistic disorder. In addition, the plasma concentration of IgE-specific antibodies and total IgE were found to be statistically significantly higher in autistic participants.[61,62] Studies have supported that celiac disease and food allergies have altered intestinal permeability. In the studies of intestinal permeability and food sensitivity, the aim of the studies conducted with 21 children with autism and 42 control groups was to determine whether the passage of larger molecular size substances through

the intestinal barrier was increased in children with autism. They suggested that the increased permeability of larger molecular substances from the gut to the bloodstream could be explained by the potential for increased sensitivity to certain peptides or proteins. As a result of the studies, they found that 43% of children with autism had increased permeability compared to unaffected control group children who did not have increased permeability.[62-64] It has been suggested that, with the resulting increased permeability, food-based or similar-sized peptides entering the bloodstream may subsequently induce allergic sensitization or cause "pharmacological" effects. This study attempted to address a theory known as the "opioid excess theory."[62,65] Digestion of food containing casein and gluten produces small peptide molecules that act as exogenous opioids. In one study, peptides identified as milk-derived casomorphin and gluten-derived gliadorphin were detected in the urine of patients with schizophrenia and autism. These peptides have been shown to bind to opioid receptors *in vitro*. It is therefore presumed to cause central nervous system effects by modulating opioid levels in the brain.[62] In another study supporting the theory, the opioid peptide theory may provide a possible explanation for reports of clinical improvement when some children with autism start restrictive diets without evidence of celiac or allergic sensitivity.[66] One criticism of the theory is that these urinary peptides are also present in asymptomatic children and therefore cannot exert a physiological effect.[67]

According to a study by Scott et al.[68] on the frequency and concentration of plasma IgA and IgG antibodies to gluten and casein in autistic and schizophrenic patients and normal volunteers, a high IgA antibody to gluten or casein was found in 30% of autistic children in the titers of IgA and IgG antibodies to gluten and casein. "In a study by Reichelt and Landmark[36,69], IgA was found to have an average of 2.1 against gluten and 1.9 against casein on a 0-6 scale." IgA concentrations are dilution titration and IgG is expressed in radioallergosorbent (RAST) score. Normal anti-IgA should be 0, and normal in the RAST unit of anti-IgG is 0 to 1600. The RAST test is a blood test that determines if a person's blood contains antibodies to a certain chemical. The frequency of high IgG antibodies against which is expressed as a random test was determined as 87% in gluten and 90% in casein in patients with autism. Again, in individuals with autism, the frequency of IgA antibodies was determined as 15% for gluten and 14% for casein. In addition, the frequency of IgA antibodies to gluten was 86% and 67% to casein among schizophrenic patients. On the other hand, the frequency of IgG antibodies against gluten in schizophrenic patients was 86% and 93% against casein.[36] In a study conducted by Sun and Cade[70] with rats, it was observed that fifty-seven seconds after giving 8-casomorphine to normal rats, the rats began to run with their teeth cracking and foaming at their mouths, and then they became hostile and attacked their cage mates. A GFCF diet reduces the degree of peptide mix in both schizophrenia and autism and is linearly associated with improvement in clinical behavior due to this reduction.[71]

In conclusion, according to studies, although most of the patients who follow the gluten-casein diet show improvement, the gluten-casein diet cannot be considered a clear treatment method for patients due to the different genetic structures and environmental conditions in humans. Although applying a gluten-free diet alone does not cure the patient, more efficient results can be achieved by making a gluten-free and casein-free diet a lifestyle. Even though gluten and casein are thought to be substances that trigger these diseases, it should not be forgotten that these foods that are not included in the diet can cause serious protein, vitamin, and mineral deficiencies. First and foremost, if the diet to be applied is investigated whether the patient has gluten or casein intolerance or allergy and treatment is applied accordingly, the symptoms can be reduced or eliminated. Various antibody tests to be performed on the person will give better information about whether there is sensitivity.

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REFERENCES

1. Çetin N, Özdoğan Y, Erbaş O. Sodium Dysbiosis and Autism Spectrum Disorder. Journal of Experimental and Basic Medical Sciences. 2021;2:122-7.
2. Melini V, Melini F. Gluten-Free Diet: Gaps and Needs for a Healthier Diet. Nutrients. 2019 Jan 15;11:170.
3. Baspinar B, Yardimci H. Gluten-Free Casein-Free Diet for Autism Spectrum Disorders: Can It Be Effective in Solving Behavioural and Gastrointestinal Problems? Eurasian J Med. 2020;52:292-7.
4. Biesiekierski JR. What is gluten? J Gastroenterol Hepatol. 2017;32 Suppl 1:78-81.

5. Cebolla Á, Moreno ML, Coto L, Sousa C. Gluten Immunogenic Peptides as Standard for the Evaluation of Potential Harmful Prolamin Content in Food and Human Specimen. Nutrients. 2018 Dec 5;10:1927.
6. Hoppe C, Gøbel R, Kristensen M, Lind MV, Matthiessen J, Christensen T, et al. Intake and sources of gluten in 20- to 75-year-old Danish adults: a national dietary survey. Eur J Nutr. 2017;56:107-17.
7. Shewry P. What Is Gluten-Why Is It Special? Front Nutr. 2019;6:101.
8. Wieser H. Chemistry of gluten proteins. Food Microbiol. 2007;24:115-9.
9. Shewry PR, Tatham AS. Disulphide Bonds in Wheat Gluten Proteins. J Cereal Sci. 1997;25:207-27.
10. Hausch F, Shan L, Santiago NA, Gray GM, Khosla C. Intestinal digestive resistance of immunodominant gliadin peptides. Am J Physiol Gastrointest Liver Physiol. 2002;283:G996-G1003.
11. Junker Y, Zeissig S, Kim S-J, Barisani D, Wieser H, Leffler DA, et al. Wheat amylase trypsin inhibitors drive intestinal inflammation via activation of toll-like receptor 4. J Exp Med. 2012;209:2395-408.
12. de Punder K, Pruimboom L. The dietary intake of wheat and other cereal grains and their role in inflammation. Nutrients. 2013;5:771-87.
13. Dönmez B, Erbakan K, Erbaş O. The Role of Insulin-like Growth Factor on Autism Spectrum Disorder. Journal of Experimental and Basic Medical Sciences. 2021;2:430-5.
14. Marder SR, Cannon TD. Schizophrenia. N Engl J Med. 2019;381:1753-61.
15. Ergün C, Urhan M, Ayer A. A review on the relationship between gluten and schizophrenia: Is gluten the cause? Nutr Neurosci. 2018;21:455-66.
16. Khanna S, Tosh PK. A clinician's primer on the role of the microbiome in human health and disease. Mayo Clin Proc. 2014;89:107-14.
17. Dickerson F, Severance E, Yolken R. The microbiome, immunity, and schizophrenia and bipolar disorder. Brain Behav Immun. 2017;62:46-52.
18. Severance EG, Prandovszky E, Castiglione J, Yolken RH. Gastroenterology issues in schizophrenia: why the gut matters. Curr Psychiatry Rep. 2015;17:27.
19. Severance EG, Yolken RH, Eaton WW. Autoimmune diseases, gastrointestinal disorders and the microbiome in schizophrenia: more than a gut feeling. Schizophr Res. 2016;176:23-35.
20. Nemani K, Hosseini Ghomi R, McCormick B, Fan X. Schizophrenia and the gut-brain axis. Prog Neuropsychopharmacol Biol Psychiatry. 2015;56:155-60.
21. Dickerson F, Stallings C, Vaughan C, Origoni A, Goga J, Khushalani S, et al. Artemisinin reduces the level of antibodies to gliadin in schizophrenia. Schizophr Res. 2011;129:196-200.
22. Arling TA, Yolken RH, Lapidus M, Langenberg P, Dickerson FB, Zimmerman SA, et al. Toxoplasma gondii antibody titers and history of suicide attempts in patients with recurrent mood disorders. J Nerv Ment Dis. 2009;197:905-8.
23. Klein RS, Garber C, Howard N. Infectious immunity in the central nervous system and brain function. Nat Immunol. 2017;18:132-41.
24. Park M-H, Kwon Y-J, Jeong H-Y, Lee H-Y, Hwangbo Y, Yoon H-J, et al. Association between Intracellular Infectious Agents and Schizophrenia. Clin Psychopharmacol Neurosci. 2012;10:117-23.
25. Severance EG, Xiao J, Jones-Brando L, Sabunciyan S, Li Y, Pletnikov M, et al. Toxoplasma gondii-A Gastrointestinal Pathogen Associated with Human Brain Diseases. Int Rev Neurobiol. 2016;131:143-63.
26. Severance EG, Kannan G, Gressitt KL, Xiao J, Alaedini A, Pletnikov MV, et al. Anti-gluten immune response following Toxoplasma gondii infection in mice. PLoS One. 2012;7:e50991.
27. Severance EG, Gressitt KL, Yang S, Stallings CR, Origoni AE, Vaughan C, et al. Seroreactive marker for inflammatory bowel disease and associations with antibodies to dietary proteins in bipolar disorder. Bipolar Disord. 2014;16:230-40.
28. Li Y, Weber NS, Fisher JA, Yolken RH, Cowan DN, Larsen RA, et al. Association between antibodies to multiple infectious and food antigens and new onset schizophrenia among US military personnel. Schizophr Res. 2013;151:36-42.
29. Yoshikawa M. Exorphin-opioid active peptides of exogenous origin. Handbook of Biologically Active Peptides. Elsevier; 2006.pp.1365-71.
30. Fukudome S, Yoshikawa M. Opioid peptides derived from wheat gluten: their isolation and characterization. FEBS Lett. 1992 Jan 13;296:107-11.
31. Jarmołowska B, Teodorowicz M, Fiedorowicz E, Sienkiewicz-Szłapka E, Matysiewicz M, Kostyra E. Glucose and calcium ions may modulate the efficiency of bovine β-casomorphin-7 permeability through a monolayer of Caco-2 cells. Peptides. 2013;49:59-67.
32. Kurek M, Przybilla B, Hermann K, Ring J. A naturally occurring opioid peptide from cow's milk, beta-casomorphine-7, is a direct histamine releaser in man. Int Arch Allergy Immunol. 1992;97:115-20.
33. Klee WA, Zioudrou C, Streaty RA. Exorphins: peptides with opioid activity isolated from wheat gluten, and their possible role in the etiology of schizophrenia. In: Usdin E, Bunney WE, Kline NS, editors. Endorphins in Mental Health Research. London: Palgrave Macmillan UK; 1979.pp.209-18.
34. Dohan FC. Genetic hypothesis of idiopathic schizophrenia: its exorphin connection. Schizophr Bull. 1988;14:489-94.
35. Erbaş O, Erdoğan MA, Khalilnezhad A, Solmaz V, Gürkan FT, Yiğittürk G, et al. Evaluation of long-term effects of artificial sweeteners on rat brain: a biochemical, behavioral, and histological study. Journal of Biochemical and Molecular Toxicology. 2018. p. e22053.
36. Cade R, Privette M, Fregly M, Rowland N, Sun Z, Zele V, et al. Autism and Schizophrenia: Intestinal Disorders. Nutr Neurosci. 2000;3:57-72.
37. Dohan FC, Grasberger JC, Lowell FM, Johnston HT Jr,

Arbegast AW. Relapsed schizophrenics: more rapid improvement on a milk- and cereal-free diet. Br J Psychiatry. 1969;115:595-96.
38. Rice JR, Ham CH, Gore WE. Another look at gluten in schizophrenia. Am J Psychiatry. 1978;135:1417-18.
39. Vlissides DN, Venulet A, Jenner FA. A double-blind gluten-free/gluten-load controlled trial in a secure ward population. Br J Psychiatry. 1986;148:447-52.
40. Potkin SG, Weinberger D, Kleinman J, Nasrallah H, Luchins D, Bigelow L, et al. Wheat gluten challenge in schizophrenic patients. Am J Psychiatry. 1981;138:1208-11.
41. Clappison E, Hadjivassiliou M, Zis P. Psychiatric Manifestations of Coeliac Disease, a Systematic Review and Meta-Analysis. Nutrients. 2020 Jan 4;12:142.
42. McLean RT, Wilson P, St Clair D, Mustard CJ, Wei J. Differential antibody responses to gliadin-derived indigestible peptides in patients with schizophrenia. Transl Psychiatry. 2017;7:e1121.
43. Rashid M, Butzner JD, Warren R, Molloy M, Case S, Zarkadas M, et al. Home blood testing for celiac disease: recommendations for management. Can Fam Physician. 2009;55:151-3.
44. Bounous G, Kongshavn PA, Taveroff A, Gold P. Evolutionary traits in human milk proteins. Med Hypotheses. 1988;27:133-40.
45. Joy JM, Vogel RM, Shane Broughton K, Kudla U, Kerr NY, Davison JM, et al. Daytime and nighttime casein supplements similarly increase muscle size and strength in response to resistance training earlier in the day: a preliminary investigation. J Int Soc Sports Nutr. 2018;15:24.
46. Park S-W, Kim J-Y, Kim Y-S, Lee SJ, Lee SD, Chung MK. A milk protein, casein, as a proliferation promoting factor in prostate cancer cells. World J Mens Health. 2014;32:76-82.
47. Müller-Buschbaum P, Gebhardt R, Roth SV, Metwalli E, Doster W. Effect of calcium concentration on the structure of casein micelles in thin films. Biophys J. 2007;93:960-8.
48. Institute of Medicine (US) Committee to Review Dietary Reference Intakes for Vitamin D and Calcium. Dietary Reference Intakes for Calcium and Vitamin D. Ross AC, Taylor CL, Yaktine AL, Del Valle HB, editors. Washington (DC): National Academies Press (US);2011.
49. Woodford KB. Casomorphins and Gliadorphins Have Diverse Systemic Effects Spanning Gut, Brain and Internal Organs. Int J Environ Res Public Health. 2021 Jul 26;18:7911.
50. Szilagyi A, Ishayek N. Lactose Intolerance, Dairy Avoidance, and Treatment Options. Nutrients. 2018 Dec 15;10:1994.
51. Salzberg, H.K. Casein glues and adhesives. In Handbook of Adhesion, 2nd ed.; Van Nostrand Reinhold Company: New York, NJ, USA, 1977;pp.158-71.
52. Marí-Bauset S, Zazpe I, Mari-Sanchis A, Llopis-González A, Morales-Suárez-Varela M. Evidence of the gluten-free and casein-free diet in autism spectrum disorders: a systematic review. J Child Neurol. 2014 Dec;29:1718-27.
53. Bell SJ, Grochoski GT, Clarke AJ. Health implications of milk containing beta-casein with the A2 genetic variant. Crit Rev Food Sci Nutr. 2006;46:93-100.
54. Severance EG, Dupont D, Dickerson FB, Stallings CR, Origoni AE, Krivogorsky B, et al. Immune activation by casein dietary antigens in bipolar disorder. Bipolar Disord. 2010;12:834-42.
55. Faras H, Al Ateeqi N, Tidmarsh L. Autism spectrum disorders. Ann Saudi Med. 2010 Jul-Aug;30:295-300.
56. Erbas O, Erdogan MA, Khalilnezhad A, Gürkan FT, Yiğittürk G, Meral A, et al. Neurobehavioral effects of long-term maternal fructose intake in rat offspring. Int J Dev Neurosci. 2018;69:68-79.
57. Eggett A. What is Autism Spectrum Disorder? Groupwork for Children with Autism Spectrum Disorder. Routledge; 2018.pp.1-18.
58. Yücel U, Kahramanoğlu İ, Altuntaş İ, Erbaş O. Effect of mitochondrial dysfunction and oxidative stress on the pathogenesis of autism spectrum disorders. D J Tx Sci 2021;6:73-85.
59. Ekmekçi AM, Erbaş O. The role of intestinal flora in autism and nutritional approaches. Demiroğlu Bilim Üniversitesi Florence Nightingale Transplantasyon Dergisi. 2020;5:61-9.
60. Lucarelli S, Frediani T, Zingoni AM, Ferruzzi F, Giardini O, Quintieri F, et al. Food allergy and infantile autism. Panminerva Med. 1995;37:137-41.
61. Trajkovski V, Petlichkovski A, Efinska-Mladenovska O, Trajkov D, Arsov T, Strezova A, et al. Higher Plasma Concentration of Food-Specific Antibodies in Persons With Autistic Disorder in Comparison to Their Siblings. Focus Autism Other Dev Disabl. 2008;23:176-85.
62. Buie T. The relationship of autism and gluten. Clin Ther. 2013;35:578-83.
63. d'Eufemia P, Celli M, Finocchiaro R, Pacifico L, Viozzi L, Zaccagnini M, et al. Abnormal intestinal permeability in children with autism. Acta Paediatr. 1996;85:1076-79.
64. Rodop BB, Başkaya E, Altuntaş İ, Erbaş O. Nutrition Effect on Autism Spectrum Disorders. Journal of Experimental and Basic Medical Sciences. 2021;2:7-17.
65. Panksepp J. Brain opioids: A neurochemical substrate for narcotic and social dependence. Progress in theory in psychopharmacology. 1981;1:149-75.
66. Shattock P, Kennedy A, Rowell F, Berney T. Role of neuropeptides in autism and their relationships with classical neurotransmitters. Brain Dysfunction. 1990;3:328-45.
67. Reichelt WH, Ek J, Stensrud M, Reichelt KL. Peptide excretion in celiac disease. J Pediatr Gastroenterol Nutr. 1998;26:305-9.
68. Scott H, Rognum TO, Midtvedt T, Brandtzaeg P. Age-related changes of human serum antibodies to dietary and colonic bacterial antigens measured by an enzyme-linked immunosorbent assay. Acta Pathol Microbiol Immunol Scand C. 2009;93C:65-70.
69. Reichelt KL, Landmark J. Specific IgA antibody increases in schizophrenia. Biol Psychiatry. 1995;37:410-13.
70. Sun Z, Cade JR. A Peptide Found in Schizophrenia and

Autism Causes Behavioral Changes in Rats. Autism. 1999;3:85-95.

71. Cade R, Wagemaker H, Privette RM, Fregly MJ, Rogers J, Orlando J. The effect of dialysis and diet on schizophrenia. Psychiatry: A world perspective. 1990;3:494-500.