NARRATIVE REVIEW

A narrative review on manifestations of gluten free casein free diet in autism and autism spectrum disorders

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Abstract

Autism and Autism Spectrum Disorder (ASD) are specific neurological disorders that affect the brain, frequently characterised by challenging paediatric behaviour. The current narrative review using PubMed and Google Scholar was conducted in line with the Preferred Reporting Items for Systematic review and Meta-Analysis Protocols, and comprised randomised controlled trials and clinical control trials with gluten-free, casein-free (GFCF) diets published till 2020. Of the 80 studies selected, 7(8.75%) were included in the review. It was observed that the gluten-free, casein-free diet was safe with therapeutic benefits in autistic children. Therefore, a tailored dietary approach can be a beneficial management regimen. The trials related to utility of gluten-free, casein-free diet among autistic children are sparse, with limited sampling size, and indication of bias in the findings. Therefore, larger cohort studies on gluten-free, casein-free trials are required to provide further insight into the therapeutic benefits of the diet.

Keywords: Autism, Autism spectrum disorder, Gluten-free and casein-free diet, Randomised controlled trial.

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Introduction

Autism is a neurodevelopmental disorder frequently characterised by challenging social behaviour and impaired linguistic skills. It is usually exhibited in the initial three years of life, but a few are diagnosed after the age of five years.[1] It is observed that autistic children lack the ability to properly digest proteins, mainly casein and gluten, leading to synthesis of brain-altering harmful compounds, like opioid peptides, and their elevated systematic levels lead to manifestation of perplexing behaviour.[2] Casein, a phosphor-protein, is obtained from animal sources, like milk and dairy products, while gluten is derived from plant sources belonging to the grass family of wheat, oats and rye.[3] Both the proteins share a similar molecular structure and, as explained earlier, their incomplete digestion may result in the production of exorphins or exogenous opioid peptides. Exorphins generating from gluten and casein include gluteomorphins/ghadorphin and casomorphins, respectively, which are permeable to gut lumen and blood-brain barrier exerting central opioid-like actions, leading to bewildered and disconcerted behaviour.[4] Therefore, a diet exclusive of casein and gluten may facilitate the elimination of opioid peptides from the body, assisting in the diminution of autistic symptoms.[5]

Research conducted in Arizona in 2005 showed that children and adults with autism/autism spectrum disorders (ASDs) often exhibit nutritional deficiencies, metabolic imbalances, gustatory concerns and abdominal impediments, directly influencing physical growth, neurological development and sustenance. Several nutritional and dietary interventional trials have shown mitigation of these debilitating underlying disorders through scrupulously tailored dietary approach.[6]

A study conducted in New York in 2015 suggested that therapeutic dietary interventions are provided to use by approximately 15-38% of autistic children worldwide. The most prevalent dietary intervention known is the gluten-free/casein-free (GFCF) diet which comprises food devoid of gluten and casein.[7] With the findings of another interesting fact in autistic children of having leaky gut, which allows permeability of undigested food, microorganisms and contaminants to portal circulation further strengthens the established concept of absorption of partially digested protein by-products, especially opiates in blood, leading to behavioural deficits in such children.[8] As gluten and casein proteins cannot be properly digested in the gut of the affected children, the emergence of GFCF diet came to prominence to facilitate the mitigation of stunted physical and mental growth of children with autism and ASDs.[9,10]

Materials and Methods

The narrative review included interventions on the utility of GFCF diet for the management of autism/ASDs through randomised controlled trials (RCTs) and clinical controlled trials (CCTs) published in any language between 1999 and 2020. The review was carried out in accordance with the updated guidelines for Preferred Reporting Items for Systematic review and Meta-Analysis Protocols (PRISMA-

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P).[11] The search engines included PubMed and Google Scholar, and the literature search was done using the terms: "Autism" Or "Autism Spectrum Disorder" Or "Paediatric Autism and "Diet" And "Casein Free" Or/And "Gluten Free" And "Randomised Control Trial".

The databases were scanned separately by two senior researchers for studies based on their titles and abstracts, accompanied by a sampling of complete texts. Via discussion between the authors, all disagreements were resolved.

The studies included were those published in any language between 1999 and 2020 evaluating the effectiveness of GFCF diet through RCTs and CCTs in which the dependent variable needed to be correlated with autism/ASD behavioural symptoms. Also, the included articles were original comparative studies, involved a control group, and delivered adequate detail on methods and results.

The studies excluded were studies that were not RCTs or CCTs, and so were books, conference papers, theses, editorials, case notes, case studies, analyses and publications without full text. Reviews, meta-analyses, in vitro studies and studies on non-human subjects were also eliminated.

A data extraction form was used to extract the following information: research design, demographic variables analysed, description of the experiment, its duration, progress measures, measurement methods, and qualitative and quantitative data.

The included studies were finally assessed for suitability under the National Institutes of Health (NIH) RCT scoring criteria 12, and the studies were graded as excellent, good and fair.

The initial classification of quality evidence was established from the research design of RCTs and CCTs. Aspects that could minimise or improve the quality were also investigated from the original classification. Methodological limitations, inconsistencies, unreliable proof, inaccuracy, and publication bias, like factors responsible for decrease in the degree of evidence, were also noted. Treatment-response gradient, wide gradient magnitude and residual confounders were also evaluated from the trials.

Results

The search identified a total of 80 studies; 9(11.25%) on PubMed and 71(88.75%) on Google Scholar. Of the total, 7(8.75%) were selected as potentially relevant (Figure). Of the studies reviewed, 6(85.7%) were graded as excellent and 1(14.3%) as fair (Table-1). The studies used Autism Treatment Evaluation Checklist (ATEC), the Behavioural Summarised Evaluation (BSE), the Aberrant Behaviour Checklist (ABC) scales to check disease severity (Table-2).

A randomised double-blinded trial for the determination of effectiveness of GFCF diet in treating autism[10 included 15 children ranging in age from 2 to 16 years, and established the foundation of the GFCF as beneficial in the diminution of autistic behaviour, and provided prospective research directions for future studies.

Another randomised placebo trial[13] found that the treatment group receiving GFCF diet improved significantly compared to the control group. A total of 67 subjects were enrolled, including 50 non-signing neurotypicals of similar age and gender as controls and treatment subjects with ASD aged 3-58 years. It was observed that a combination of dietary supplements with

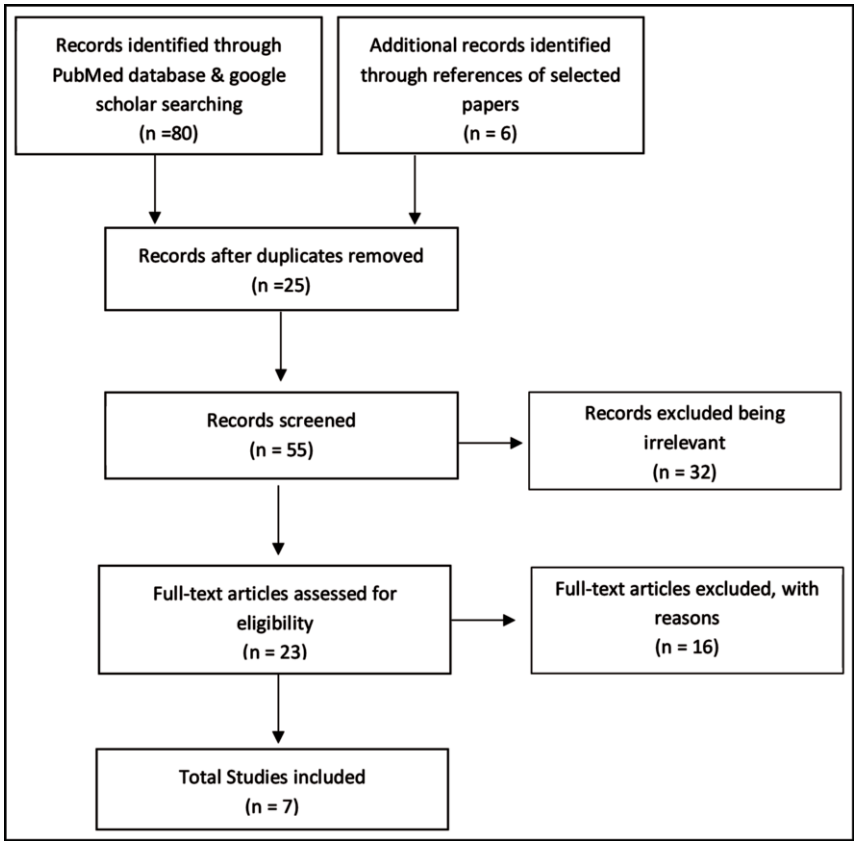

Figure: Preferred Reporting Items for Systematic review and Meta-Analysis (PRISMA) flow diagram.

Table-1: National Institutes of Health (NIH) scoring.[12]

Questions	Titles of Titles of Studies						
	The Gluten-Free, Casein-Free Diet In Autism: Results of A Preliminary Double Blind Clinical Trial	Comprehensive Nutritional and Dietary Intervention for Autism Spectrum Disorder-A Randomized, Controlled 12-Month Trial	The Gluten-Free/Casein-Free Diet: A Double-Blind Challenge Trial in Children with Autism	The Scan Brit randomized controlled single-blind study of a gluten- and casein-free dietary intervention for children with autism spectrum disorders	A Randomized, Controlled Study of Dietary Intervention in Autistic Syndromes	Influence of a Combined Gluten Free and Casein Free Diet on Behaviour Disorders in Children and Adolescents Diagnosed with Autism Spectrum Disorder: A 12 Month Follow Up Clinical Trial	Impact of Casein and Gluten Free Dietary Intervention on Selected Autistic Children
1. Was the study described as randomized, a randomized trial, a randomized clinical trial, or an RCT?	.	.	.	.	.	.	_
2. Was the method of randomization adequate (i.e., use of randomly generated assignment)?(sealed, enveloped)	.	_	.	NR	_	NR	NR
3. Was the treatment allocation concealed (so that assignments could not be predicted)? Double blind	.	_	.	_	_	_	_
4. Were study participants and providers blinded to treatment group assignment?	.	.	.	_	.	_	_
5. Were the people assessing the outcomes blinded to the participants' group assignments?	.	.	.	.	.	_	_
6. Were the groups similar at baseline on important characteristics that could affect outcomes (e.g., demographics, risk factors, co-morbid conditions)?	_	.	.	.	.	.	_
7. Was the overall drop-out rate from the study at endpoint 20% or lower of the number allocated to treatment?	NR	.	_	.	NR	.	NR
8. Was the differential drop-out rate (between treatment groups) at endpoint 15 percentage points or lower?	NR	.	_	.	NR	.	NR
9. Was there high adherence to the intervention protocols for each treatment group?	.	_	.	.	.	.	.
10. Were other interventions avoided or similar in the groups (e.g., similar background treatments)?	.	.	.	.	.	.	.
11. Were outcomes assessed using valid and reliable measures, implemented consistently across all study participants?	.	.	.	.	.	.	.
12. Did the authors report that the sample size was sufficiently large to be able to detect a difference in the main outcome between groups with at least 80% power?	_	.	_	.	_	.	.
13. Were outcomes reported or subgroups analyzed pre specified (i.e., identified before analyses were conducted)?	.	NR	.	.	.	-	.
14. Were all randomized participants analyzed in the group to which they were originally assigned i.e., did they use an intention-to-treat analysis?	.	.	.	.	.	.	.
Score	13	11	11	10	9	9	6
Study Rating	Excellent	Excellent	Excellent	Excellent	Excellent	Excellent	Fair

NR: Not reported, RCT: Randomised controlled trial.

Table-2: Randomised controlled trial (RCT) studies with nutritional intervention by gluten-free and casein-free (GFCF) diet.

Ref #	Titles	Author and Year	Study type	Country	Method	Intervention	N	Mean age (years)	Assessment	Outcome	Aim	(P-value)
10	The Gluten-Free, Casein-Free Diet In Autism: Results of A Preliminary Double Blind Clinical Trial	Elder et al., 2006	Double Blind Clinical Trial	USA	Data on autistic symptoms and urinary peptide levels were collected in the subjects' homes over the 12 weeks that they were on the diet.	The sample included 15 children aged 2-16 years with ASD. Data on autistic symptoms and urinary peptide levels were collected in the subjects' homes over the 12 weeks that they were on the diet	15	7.32	CARS, and the Autism Diagnostic Interview-Revised (ADI-R).	No significant differences with CARS, ECOS, or behavioral frequencies and no signi?cant differences in grouped data for urinary peptide levels of gluten	This study tested the efficacy of a gluten-free and casein-free (GFCF) diet in treating autism using a randomized, double blind repeated measures crossover design.	0.98
13	Comprehensive Nutritional and Dietary Intervention for Autism Spectrum Disorder - A Randomized, Controlled 12-Month Trial	Adams et al., 2018	RCT	USA	Treatment began with a special vitamin/ mineral supplement, and additional treatments were added sequentially, including essential fatty acids, Epsom salt baths, carnitine, digestive enzymes, and a healthy gluten-free, casein-free, soy-free (HGCSF) diet	Participants were recruited for the study from October 2011 to April 2014. Enrollment Criteria - Neuro typical Group. The PGI-2 was assessed at month, 3, 6, 9, and 12 for the treatment group, and at month 12 for the non-treatment group.	67	32.5	ADOS/CARS-2/Reynolds Intellectual Assessment Scales (RIAS)/Severity of Autism Scale (SAS-Pro) assessment	The treatment group improved significantly more than the no treatment group.	A combination of nutritional and dietary interventions will be effective in reducing the symptoms of autism, reducing gastrointestinal problems, and increasing overall functioning level	0.03
7	The Gluten-Free/ Casein-Free Diet: A Double-Blind Challenge Trial in Children with Autism	Hyman et al., 2016	Double-Blind Challenge Trial	USA	Obtained baseline data on children's behavioural and nutritional status. Implemented the GFCF diet over 2 weeks, maintained it for at least four more weeks with weekly nutritional monitoring, and then re-assessed behavioural and nutritional status	Dietary challenges were delivered via weekly snacks that contained gluten, casein, gluten and casein, or placebo.	14	4	Autism Diagnostic Interview and Autism Diagnostic Observation Schedule. Mullen Scales of Early Learning (Mullen 1995) Vineland Adaptive Behaviour Scales.	Study does not provide evidence to support general use of the GFCF diet.	To obtain information on the safety and efficacy of the gluten-free/ casein-free (GFCF) diet	0.002
9	The Scan Brit randomized controlled single-blind study of a gluten-and casein-free dietary intervention for children with autism	P. Whiteley et al., 2010	RCT Single-blind study	Norway	Participants were tested at baseline, 8, and 12 months. Based on per protocol repeated measures analysis, data for 26 diet	Gluten- and casein-free dietary intervention	73	7	Autism Diagnostic Observation Schedule (A DOS) and the Gilliam Autism Rating Scale (GARS), Behaviors, Vinel and Adaptive	Dietary intervention may positively affect developmental outcome for some children diagnosed with ASD.	Dietary intervention may positively affect development al outcome for some children with ASD.	0. 01

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	spectrum disorders				children and 29 controls were available at 12 month.				Behavior Scales (VABS), and Attention Deficit Hyperactivity Disorder-IV scale (ADHD-IV)		
14	A Randomized, Controlled Study of Dietary Intervention in Autistic Syndromes	A. M. Knivsberg, Reichelt, Høien, & Nødland, 2002	RCT	Norway	A randomly selected diet and control group with 10 children in each group participated. Observations and tests were done before and after period of 1 year. All the participants had autistic syndromes and also abnormal urinary peptide patterns (urinary peptide were tested)	Dietary Intervention (gluten and casein-free diet)	392	7.3	Leiter International Performance Scale (Leiter, 1979), ITPA, Illinois Test of Psycholinguistic Abilities, DIPAB (Haracopos and Kelstrup, 1975), a standardized Danish scheme	The development for the group of children on diet was significantly better than for the controls	To evaluate effect of gluten and casein-free diet for children with autistic syndromes and urinary peptide abnormalities	0.008 0.014 0.046
15	Influence of a Combined Gluten Free and Casein Free Diet on Behavior Disorders in Children and Adolescents Diagnosed with Autism Spectrum Disorder: A 12 Month Follow Up Clinical Trial	González-Domenech et al., 2020	A 12 Month Follow Up Clinical Trial	Southern Spain	Patients were evaluated at three time-points (at the beginning of the study, after normal diet and after GFCF diet). Questionnaires regarding behavior and autism and dietary adherence were completed and urinary beta-casomorphin concentrations were determined at each time-point. (Crossover clinical trial).	Gluten-and casein-free dietary intervention	40	10	Autism Treatment Evaluation Checklist (ATEC) scale, (Evaluation Resumé du Comportment, in French) Behavioral Summarized Evaluation (ERC-III) scale., Aberrant Behavior Checklist (ABC) Scale.	Nutritional intervention by gluten-free and casein-free (GFCF) diet	To determine the influence of a GFCF diet on behaviour disorders in children and adolescents diagnosed with ASD and the potential association with urinary beta-casomorphin concentrations.	0.05
5	Impact of Casein and Gluten Free Dietary Intervention on Selected Autistic Children	Peerkhan et al., 2008	Original Article	India	Diet counseling regarding casein free diet was imparted to Group I (n=10), gluten free diet to Group II (n=10) and and both casein and gluten free diet for Group III (n=10). The diet was followed for a period of 2 months. Three special schools, namely SIMEC (School I), MMIC (School II) and C.S.I. (School III) were selected by purposive sampling method	Casein and Gluten Free Dietary Intervention. The diet was followed for a period of 2 months.	50	7	The diet was followed for a period of 2 months. The efficacy of the dietary exclusion of casein and gluten was evaluated using a food and behavior diary on a day to day basis, using observation method.	The impact of dietary intervention made using dietary guide books found to be useful to reduce various behavior symptoms	Impact of Casein and Gluten Free Dietary Intervention on autistic child	-

CARS: Childhood autism rating scale, ADOS: Autism diagnostic observation schedule, ASD: Autism spectrum disorder.

balanced diet were successful in minimising autism symptoms and gastrointestinal disorders, leading to enhanced emotional, behavioural, cognitive and learning abilities.

Another RCT[7] was conducted with 14 autistic children aged 3-5 years for the determination of safety and effectiveness of the GFCF diet. It was found that the GFCF diet, when combined with nutritional therapy, improved mental wellbeing in the affected children.

Another RCT[9] suggested the utility of the GFCF diet for better developmental outcomes in ASD children.

A single-blind study to assess the effectiveness of GFCF diet for autistic children and the prevalence of urinary peptide abnormalities among them revealed that children who were placed on a GFCF diet performed better than those who were not.[14]

Another RCT comprised complementary treatments, such as GFCF diets, that are widely used in the absence of effective drugs for ASDs. The researchers wanted to see if the GFCF diet influenced behaviour problems in ASD individuals, and if there was a connection between urinary beta-casomorphin levels and behaviour problems. This crossover analysis included a total of 37 patients. Each patient followed a normal diet, including gluten and casein, for six months before switching to GFCF diet for another six months. The treatment order (normal diet first or GFCF diet first) was chosen at random. The patients were evaluated at three different points in time; at the beginning of the study, after normal diet, and after GFCF diet. Questionnaires on behaviour, autism, and dietary adherence were completed at each time point, as well as urinary beta-casomorphin concentrations were measured. There were no major behavioural changes or correlations with urinary beta-casomorphin concentrations following the GFCF diet. There were no important effects of a 6-month GFCF diet on autism developmental symptoms or urinary beta-casomorphin concentrations.[15]

Another RCT investigated the impact of dietary intervention using dietary guidebooks on autistic children's behavioural symptoms. Some autistic behavioural deficits were found improved in the GFCF diet community, including improved concentration, improved sleeping habits, and hyperactive and anxious behaviour.[5]

Discussion

Healthcare systems continue to confront the accelerating and complex problem of ASDs. Autism's emotional variation varies from person to person, making management challenging and necessitating personalised treatment. The advantages of dietary intervention are greater as symptomatic changes were seen after a properly followed GFCF diet, laying the groundwork for a diet that will undoubtedly benefit the affected children.[5]

The current narrative review indicates that there is a dearth of data in this area, both in terms of quality and quantity. This is based on several limitations discovered, particularly those related to scarcity and uncertainty of available data, such as methodological limitations linked to a variety of factors, such as the lack of a control group, unclear definitions of inclusion criteria, very small sample sizes and examinations based on single individuals, heterogeneous groups in terms of age, and so on. There was also the possibility that data on behavioural variables could be skewed over time due to memories of parents and other relatives, and that these changes in participant behaviour could be influenced even more by the fact that they were participating in non-blinded study trials.[16]

Gonzalez-Domenech et al. conducted an RCT involving autistic children, and, after 6 months of dietary intervention, found no substantial amount of beta-casomorphin in the urine of autistic children, indicating that the GFCF diet had no effect on them. Similarly, a placebo effect may have influenced the results. Finally, such predispositions as the likelihood of confounding bias can be related to mental improvements as a result of continuous learning and behavioural therapy, rather than to the GFCF diet.[15]

Knivsberg et al. conducted a single-blind controlled study having 20 autistic children. After a year, findings and experiments were performed which showed that people in the diet group had substantially less autistic behaviour than those in the control group.[17]

Previously, a systematic review concluded that there is a lack of evidence supporting the use of the GFCF diet for ASD treatment. It looked at 6 RCTs that were not blinded and a single-blind RCT, and concluded that data was insufficient to draw a valid conclusion since most of the studies lacked a control group.[18] Another systematic analysis found that removing the GFCF diet did not result in a substantial increase in ASD symptoms. Moreover, it stated that 3 of the 5 studies concluded that GFCF diet was not beneficial for autistic patients.[19] Millward et al. in 2008 found an important effect of GFCF diet on autistic traits, pointing out wider confidence intervals in the study outcomes.[20] Another research, published in 2013, was similar to earlier systematic reviews in stressing the possibility that incorrect and insufficient data about the GFCF diet could be linked to genetic variances among

people with ASD.[21]

The current narrative review did not include any study conducted on autistic individuals in Pakistan as there is lack of data at the national level. As such, the findings cannot be generalised to Pakistani population. Large-scale clinical trial or research must be done with adjuvant therapy of non-pharmacological diet in the country.

Conclusion

Huge family data is required to increase the research momentum. Also, there is a need to collect large dietary intervention data to analyse the results.

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