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REVIEW

A review of gluten- and casein-free diets for treatment of autism: 2005–2015

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Background: The gluten-free, casein-free (GFCF) diet is heralded by strong anecdotal parental reports to greatly improve and even "cure" symptoms of autism spectrum disorders (ASDs). Yet, to date, little conclusive empirical evidence exists supporting its use.

Objective: The purpose of this paper is to provide an overview of the state of the recent evidence regarding the use of GFCF diet for treatment of individuals with ASD.

Methods: Five database providers (PubMed, Web of Knowledge, EBSCO, ProQuest, and WorldCat) were used to search 19 databases, yielding a total of 491 articles that were published through February 2015. Peer-reviewed articles published between January 2005 and February 2015 were included for review if study participants were identified as having ASD and if the study investigated the effects of the GFCF diet on ASD behaviors or the relationship between the diet and these behaviors.

Results: Evaluation of search results yielded eleven reviews, seven group experimental studies including five randomized controlled trials, five case reports, and four group observational studies published during the last 10 years. These studies represent a marked increase in the number of reported studies as well as increased scientific rigor in investigation of GFCF diets in ASD.

Conclusion: While strong empirical support for the GFCF diet in ASD is currently lacking, studies point to the need for identifying subsets of individuals (eg, those with documented gastrointestinal abnormalities) who may be the best responders to the GFCF diet. Identifying these subsets is critically needed to enhance rigor in this research area. Until rigorous research supporting the use of GFCF diet is reported, clinicians should continue to use caution and consider several factors when advising regarding implementation of the GFCF diet for individuals with ASD.

Keywords: GFCF diet, autism spectrum disorders, review, gluten free, casein free, dietary intervention

Introduction

Autism, or the broader category of autism spectrum disorder (ASD), continues to pose challenges in determining the most efficacious and effective treatment approaches for managing associated social, communication, behavioral, and developmental symptoms.[1] First described in a 1943 case report by Kanner,[2] interventional approaches for autism have been the subject of a vast number of clinical reports and case studies; less common are rigorous intervention trials. Recently, the thinking about ASD has expanded from a solely psychiatric condition to a multisystem inflammatory disorder that includes systemic inflammation of the gastrointestinal (GI) tract impacting the brain, immune system, and metabolism.[3]

One popular treatment for addressing possible systemic inflammation is the gluten-free, casein-free (GFCF) diet, heralded by strong anecdotal parental reports of greatly improved[4] and even "cured" symptoms of ASD, such that the child no longer meets criteria for ASD.[5] The GFCF diet was first identified for use in schizophrenia,[6] where a possible genetic defect may contribute to what has been referred to as a "leaky gut", resulting in an overload of gluten (from wheat) and casein (from dairy). It is posited that this overload causes high peptide levels, which may produce an opioid-type effect that manifests in the behavioral symptoms commonly seen in ASD.[7] Others speculate that many individuals with ASD may have undiagnosed gastric conditions and sensitivities that are caused or aggravated by the ingestion of casein and gluten. This discomfort, or even severe pain in some cases, may result in externalizing behaviors (eg, tantrums, screaming, and aggression) and inattention to tasks due to the distraction because of the pain.

Several systematic reviews[8–14] of GFCF studies have focused on the few existing intervention studies and reported inconclusive results.[8–14] However, as Kanner[2] noted in his case report, a thorough review must address case studies as well as reports of clinical trials to produce a "full view of the landscape" of what is currently known about the GFCF diet. Such comprehensiveness is needed to assist families and clinical professionals in making informed decisions about implementing the GFCF diet and can identify specific directions for future research.

The purpose of this paper is to provide an overview of the state of the recent evidence regarding the use of GFCF diet for treatment of individuals with ASD as needed for directing future research and advancing clinical practice recommendations. As such, we reviewed the scientific literature published between January 2005 and February 2015 and have organized our review into four sections: summaries of review articles, group experimental intervention studies including randomized clinical trials, case reports, and group observational studies.

Methods

We began our review with a scoping search of the literature in order to gain a broad overview of the existing relevant literature. Table 1 details our search strategies, which were constructed by the third author, a research librarian. Nineteen databases from five database providers (PubMed, Web of Knowledge, EBSCO, ProQuest, and WorldCat) were searched via subject headings and keywords, with the latter truncated and/or phrase searched to capture various forms of gluten, casein, GFCF diet, autism, ASD, and Asperger's syndrome. Search efforts yielded a total of 491 articles. Removal of duplicates and non-English articles left 290 potential articles, whose titles (and abstracts when needed) were independently screened by two members of the research team. Additional screening was conducted for 1) publication date prior to 2005; 2) publication type, such as commentary, letter to the editor, book chapter, or thesis/dissertation; 3) publication in nonpeer reviewed periodical; 4) main topics unrelated to gluten- or casein-restricted diet; 5) main topics unrelated to ASD; 6) non-ASD research participants; and/or 7) non-English publications. Full texts of the remaining 61 publications were read and sorted by article type (ie, review, experimental, case, group observational). Review articles focusing on GFCF diet in ASD were retained; all remaining articles were read for major focus on use of GFCF diet in ASD. Backward searches of references in the eleven included review articles yielded one additional published abstract, resulting in the 27 publications included in our review. At each step of the article reduction process, two researchers discussed discrepancies in their independent evaluations until consensus was reached; when needed, a third member of the research team assisted with deliberations.

Review articles, intervention studies, case reports, and group observational studies were included if the study participants were identified as having ASD, and the study investigated either the effects of the GFCF diet on ASD behaviors or the relationship between the diet and behaviors of individuals with ASD. All articles included for review were published in peer-reviewed, English-language journals between January 2005 and February 2015. Studies were excluded if they did not focus on GFCF diet in ASD. However, because of the paucity of randomized controlled trials (RCTs) reported in the literature and because of the study's rigor, we chose to include the one double-blind RCT reported via published abstract[15] (no other published abstracts reported on a RCT testing GFCF diets in ASD).

Results

Reviews

A total of eleven review articles[8–14,16–19] from ten research groups were included in this review and are summarized in Table 2. Hereafter, we will refer to these eleven review articles as ten reviews because one review article was written as an addendum[11] of the group's review that was published in the prior year.[10] These authors reviewed a RCT reported in 2010 by Whiteley et al,[20] which was published shortly after the original review was released. Notably, six[12–14,17–19]

Table 1 Search strategies used

Database (provider)	Search strategy	Limits	Date searched	Number of results
PubMed	((diet OR dietary) AND (restrict OR restricts OR restricted OR restriction OR restrictions OR limit OR limits OR limited OR limitation OR limitations)) AND ("ASD"[tiab] OR "Child Development Disorders, Pervasive"[Mesh] OR "Asperger Syndrome"[Mesh] OR Asperger[tiab] OR Asperger'[tiab] OR Asperger's[tiab] OR Aspergers[tiab] OR Aspergers's[tiab] OR autism[tiab] OR autistic[tiab] OR "Autistic Disorder"[Mesh])	Clinical trial; review; evaluation studies; journal article; twin study; published in the last 10 years; English	2/28/15	86
PubMed	(("gluten free" AND "casein free") OR "GFCF"[tiab] OR "gluten free casein free") AND ("ASD"[tiab] OR "Child Development Disorders, Pervasive"[Mesh] OR "Asperger Syndrome"[Mesh] OR Asperger[tiab] OR Asperger'[tiab] OR Asperger's[tiab] OR Aspergers[tiab] OR Aspergers's[tiab] OR autism[tiab] OR autistic[tiab] OR "Autistic Disorder"[Mesh] OR "Child Development Disorders, Pervasive"[Mesh]))	Published in the last 10 years; English	2/28/15	42
Academic Search Premier (EBSCO)	(DE "Gluten-free diet" OR DE "Casein-free diet" OR ("gluten free diet*" OR "gluten free" OR "casein free diet*" OR "casein-free" OR GFCF OR GFD OR "gluten* and casein-free diet*" OR ((gluten OR casein) AND ("restricted diet*" OR "diet* restriction*"))) AND AB (autis* OR ASD OR ASC OR "autism spectrum disorder*" OR "autism spectrum condition*") OR TI (autis* OR ASD OR ASC OR "autism spectrum disorder*" OR "autism spectrum condition*")	Scholarly (peer-reviewed journals)	3/17/15	43
CINAHL (EBSCO)	(MH "Autistic Disorder" OR MH "Asperger Syndrome" OR autis* OR ASD OR ASC OR Asperger*) AND MH "Diet, Gluten-Free" OR GFD OR ((MH "Diet" OR "diet* restriction*" OR "restricted diet*" OR "limited diet*" OR "diet* limit*") AND ("gluten free" OR gluten OR casein OR "casein free" OR GFCF))	2004–2014; academic journals; English	3/18/15	22
Education Full Text (HW Wilson on EBSCO)	GFD OR ((gluten OR "gluten free" OR "gluten-free" OR casein OR "casein free" OR "casein-free" OR GFCF) AND (diet* OR "diet* restriction*" OR "restricted diet*" OR "limited diet*" OR "diet* limit*")) AND (DE "Autism spectrum disorders" OR DE "Asperger's syndrome" OR DE "Autism" OR DE "Autism spectrum disorders in women" OR DE "Pervasive developmental disorder not otherwise specified" OR ASD OR ASC OR autis*)	2003–2014; scholarly, peer-reviewed academic journals	3/18/15	5
Health source: Nursing/Academic Edition (EBSCO)	(DE "Autism spectrum disorders" OR DE "Autism" OR DE "Pervasive developmental disorder not otherwise specified" OR autis* OR Asperger* OR ASD OR ASC) AND ((DE "Gluten-free diet" OR DE "Casein-free diet" OR ((gluten OR "gluten free" OR casein OR "casein free" OR GFCF) AND (diet* OR "diet* limit*" OR "limited diet*" OR "diet* restriction*" OR "restricted diet*")))	Peer-reviewed academic journals or reviews, 1997–2014	3/18/15	24
Psychology and Behavioral Sciences Collection (EBSCO)	DE "Autism spectrum disorders" OR DE "Asperger's syndrome" OR DE "Autism" OR autis* OR ASD OR ASC) AND (((DE "Diet" OR DE "Diet therapy") AND (gluten OR "gluten-free" OR casein OR "casein-free" OR GFCF)) OR GFD OR DE "Casein-free diet" OR DE "Gluten-free diet")	1978–2014 publication date; peer-reviewed and academic journals	3/18/15	34
PsycINFO (EBSCO)	(DE "Aspergers Syndrome" OR DE "Autism" OR "autism spectrum disorder*" OR "autism spectrum condition*" OR ASD OR ASC OR autis*) AND ((DE "Dietary Restraint" OR DE "Diets" OR "diet* restriction*" OR "restricted diet*" OR "diet* limitation*" OR "limited diet*") AND (gluten OR casein OR GFCF OR GFD OR "gluten-free" OR "casein free"))	Academic journals, books, and dissertations	3/18/15	35
SportDiscus (EBSCO)	(DE "Casein-free diet" OR DE "Gluten-free diet" OR (DE "Diet in disease" OR DE "Diet therapy" OR DE Nutritionally induced diseases" OR DE "Diet" OR "diet* restriction*" OR "restricted diet*" OR "diet* limitation*" OR "limited diet*) AND (DE "Gluten-free foods" OR gluten OR "gluten free" OR casein OR "casein free") AND (Asperger* OR ASD OR ASC OR autis* OR "autism spectrum disorder*" OR "autism spectrum condition*")	Academic journals, 2002–2014	3/18/15	8
Web of Science (Web of Knowledge)	("gluten* and casein-free diet*" OR (("gluten free" OR "casein free" OR GFCF OR gluten OR casein) AND ("restricted diet*" OR "diet* restriction*" OR "limited diet*" OR "diet* limit*"))) AND TOPIC: (autis* OR ASD OR ASC OR "autism spectrum disorder*" OR Asperger*)	No limits set	3/18/15	21

(*Continued*)

Table 1 (*Continued*)

Database (provider)	Search strategy	Limits	Date searched	Number of results
ASSIA (ProQuest)	((SU.EXACT("Diet" OR diet*) AND (gluten* OR casein* OR GFC OR GFCF)) AND ((SU.EXACT. EXPLODE("Autistic spectrum disorders") OR SU.EXACT EXPLODE ("Autism" OR "infantile autism") OR SU.EXACT. EXPLODE("Asperger's syndrome")) OR ASD OR autis* OR Asperger*)	No limits set	3/27/15	6
Dissertations and Theses (ProQuest)	diet* AND (gluten* OR casein* OR GFC OR GFCF) AND (autis* OR ASD OR Asperger*). Narrowed by Subject: biochemistry; genetics; microbiology; cellular biology; food science; medicine; autism; livestock; toxicology; analytical chemistry; anatomy and physiology; biology; health care management; nursing; occupational therapy; alternative medicine; parents and parenting; rehabilitation; therapy =247 results, 5 selected as relevant	No limits set	3/27/15	5
ERIC (ProQuest)	(SU.EXACT.EXPLODE("Pervasive Developmental Disorders") OR ASD OR autism* OR Asperger*) AND ((SU. EXACT.EXPLODE("Dietetics") OR diet*) AND (gluten* OR casein* OR GFD OR GFCF))	No limits set	3/27/15	23
Agricola (ProQuest)	(gluten* OR casein* OR GFD OR GFCF) AND (autis* OR Asperger* OR ASD) AND diet*	No limits set	3/29/15	9
SportDiscus (EBSCO)	((DE "Diet" OR DE "Diet in disease" OR DE "Diet therapy" OR DE "Nutritionally induced diseases") OR diet*) AND (gluten* OR casein* OR GFD OR GFCF) AND (autis* OR Asperger* OR ASD	Academic journals, 2002–2014	3/29/15	9
Alt HealthWatch (EBSCO)	((DE "DIET") OR (DE "NUTRITIONALLY induced diseases") OR (DE "DIET in disease") OR (DE "DIET therapy") OR diet*) AND (gluten* OR casein* OR GFD OR GFCF) AND (DE "AUTISM spectrum disorders" OR DE "ASPERGER'S syndrome" OR DE "AUTISM" OR autis* OR Asperger* OR ASD)	No limits set	3/29/15	6
PubAg	(gluten* OR casein* OR GFCF OR GFD) AND diet* AND (autis* OR ASD OR Asperger*)	No limits set	3/29/15	0
BIOSIS (Web of Knowledge)	TOPIC: (gluten* OR casein* OR GFD OR GFCF) AND TOPIC: (diet*) AND TOPIC: (autis* OR Asperger* OR ASD)	No limits set	3/29/15	57
CABI (Web of Knowledge)	TOPIC: (diet*) AND TOPIC: (autis* OR ASD OR Asperger*) AND TOPIC: (casein* OR gluten* OR GFC OR GFCF)	No limits set	3/29/15	27
Dissertations and Theses (WorldCat)	(kw: gluten* OR kw: casein* OR kw: GFD OR kw: GFCF) AND kw: diet* AND (kw: autis* OR kw: ASD OR kw: Asperger*)	No limits set	3/29/15	29
Web of Science	Backward referencing from 11 review articles selected for inclusion	Not applicable	9/8–9/14/15	1

Abbreviations: AB, abstract; ASC, autism spectrum condition; ASSIA, Applied Social Sciences Index and Abstracts; ASD, autism spectrum disorder; CINAHL, cumulative index to nursing and allied health literature; DE, descriptor; ERIC, Educational Resources Information Center; GFCF, gluten-free, casein-free; GFD, gluten-free diet; MH, subject heading; TI, title

Table 2 Review articles

Study	Review type and topic(s)	Age of participants	Publication years	Number and types of studies included	Author's conclusions regarding GFCF diet in ASD
Christison and Ivany[8]	Systematic review: published trials of gluten and/or casein elimination in children with ASD.	Authors did not report ages included in search. Participant ages in included studies: 3–22 years.	Authors did not report years searched. Years of included studies: 1990–2002.	N=7. 6 uncontrolled clinical trials. 1 single-blind RCT.	Inadequate evidence to clearly support or refute use of GFCF for ASD symptom alleviation. Outcome assessments should include measurement of nonverbal cognition.
Elder et al[16]	Narrative overview review. Topics: historical background GFCF diets; GI abnormalities in ASD; evidence informing GFCF effect in ASD.	Authors did not report ages included in search or review.	Authors did not report years searched or years of included studies.	N=not reported. n=3 studies regarding effectiveness of GFCF diet in treatment of ASD. 1 systematic review. 2 RCTs.	Great need for additional research exists in order to address remaining questions from both researchers and families; great needs exist for patients with ASD and their families.
Millward et al[9]	Systematic review: published RCTs examining effectiveness of gluten- and/or casein-free diets on symptoms of individuals with ASD.	Children, adolescents, and adults included in search. Participant ages in included studies: 2–16 years.	Years searched: 1965 to April 2007. Years of included studies: 2002–2006.	N=2. 1 single-blind RCT. 1 double-blind RCT.	Authors cannot recommend gluten and/or casein exclusion diets as standard treatment of individuals with ASD. Larger well-controlled trials are needed.
Mulloy et al[10]	Systematic review: all available studies where gluten and/or casein was removed or reduced to treat ASD.	Authors did not report ages included in search. Participant ages in included studies: 2–17 years.	Authors did not report years searched. Years of included studies: 1978–2007.	N=14. 2 case observational studies. 4 group observational studies. 2 single-subject experimental studies. 6 group experimental studies.	Evidence is limited and weak in supporting use of GFCF diets for treatment of ASD. GFCF diets should only be used when behavioral changes appear to be associated with diet changes and/or in the presence of confirmed allergy to gluten and/or casein.
Mulloy et al[11]	Addendum to earlier published systematic review.	Participant ages in included study: 4 years–10 years 11 months.	Year of included study: 2010.	N=1. 1 single-blind RCT.	Researchers maintain their position as published in 2010; no new conclusions in light of the newly published study reviewed in this addendum to the systematic review conducted by Mulloy et al.[13]
Buie[17]	Narrative review: literature evaluating the use of GF diets in patients with ASD. Topics: gluten sensitivity, celiac disease, diet allergies, gut permeability, and opioid peptide theory and ASD; evidence of GFCF diet effect in treatment of ASD.	Author did not report ages included in search or review.	Years searched: 1990–2012. Author did not report years of included studies.	N=not reported. n=4 clinical trials of GFCF diet in treatment of ASD.	Insufficient evidence to support GF diet as treatment for ASD. Gluten sensitivity can present with a variety of symptoms. Identification of a subgroup of characteristic presentation may help predict response to dietary interventions. Additional considerations are needed as to what may constitute response to interventions (eg, better sleep, improved task performance) in individuals with ASD.

(*Continued*)

Table 2 (*Continued*)

Study	Review type and topic(s)	Age of participants	Publication years	Number and types of studies included	Author's conclusions regarding GFCF diet in ASD
Dosman et al[18]	Narrative exploratory review. Topics: current evidence for potential benefits of GFCF diet in children with ASD; risks of GFCF diet in children with ASD.	Authors did not report ages included in search or review.	Authors did not report years searched or years of included studies.	N= not reported. n=7 testing effect of GFCF diet in treatment of ASD. 2 systematic reviews. 3 single-blind RCTs. 2 double-blind RCTs.	Inconclusive evidence regarding GFCF diet effectiveness due to methodological limitations. Studies suggest existence of a subgroup of responders to GFCF diet.
Hurwitz[12]	Systematic review: RCTs of GFCF diet in treating ASD.	Age of participants included in search: <18 years. Participant ages in included studies: 2–16 years.	Years searched: 1999–2012. Years of included studies: 2003–2011.	N=5. 1 open RCT. 2 single-blind RCTs. 2 double-blind RCTs.	Effect of GFCF diet on behavior of children with ASD is inconclusive; GFCF diet does not significantly change functioning or behavior.
Whiteley et al[13]	Narrative review. Topics: summary of main experimental research of GFCF in ASD; main effects of GFCF diet in ASD; highlight of safety issues with dietary interventions; discussion of current explanations regarding potential dietary effect.	Authors did not report ages included in search or review.	Authors did not report years searched or years of included studies.	N= not reported. n=12 regarding effectiveness of GFCF diet in treatment of ASD. 1 survey. 3 open clinical trials. 3 single-blind RCTs. 2 double-blind RCTs. 4 systematic reviews.	Experimental studies suggest improved symptoms and improved development for some individuals with ASD. Dietary studies do not yet adequately measure GFCF diet effects having clinical significance (as opposed to statistical significance) such as effects that, if exist, positively increase quality of life and overall daily functioning.
Zhang et al[19]	Systematic research synthesis: adherence to EBP standards and effectiveness of GFCF diet for treatment of ASD.	Authors did not report ages included in search or review.	Authors did not report years searched. Years of included studies: 1977–2010.	N=23. 7 group comparison studies. 2 single subject design. 7 AB design. 7 studies did not identify research design.	Evidence insufficient to draw firm conclusions as to efficacy of GFCF diets for individuals with ASD.
Marí-Bauset et al[14]	Systematic review: gluten-free, casein-free type restrictive diets' treatment effectiveness and safety in ASD.	All ages included in the search. Participant ages in included studies: 2 years to adults.	Years searched: 1970 to September 30, 2013. Years of included studies: 1971–2012.	N=32 total. n=24 regarding effectiveness of GFCF diet in treatment of ASD. 3 observational case reports/ case series. 2 experimental case reports. 1 experimental cohort study. 1 open-label study.	Evidence is limited and weak in supporting use of GFCF diets for treatment of ASD. Authors advise against introduction of gluten-free and/or casein-free diets unless gluten and/or casein intolerance or allerg has been diagnosed. Future research can target identification of a diet-related phenotype and/or discovery of a marker for responsiveness to GFCF dietary intervention.

2 open-label experimental studies.	
2 open-label cohort studies.	
1 open-label experimental cohort study.	
1 open-label double-blind controlled cohort study.	
1 open-label randomized experimental study.	
1 double-blind randomized experimental cohort study.	
1 retrospective double-blind randomized trial.	
2 single-blind RCTs.	
3 double-blind RCTs.	
3 systematic reviews.	

Abbreviations: AB, 2 phase study where A phase is the baseline phase and B phase is the intervention phase; ASD, autism spectrum disorder; GF, gluten-free only; GFCF, gluten-free, casein-free; EBP, evidence-based practice; GI, gastrointestinal; RCT, randomized controlled trial.

of the ten reviews were published during the last 2 years of our review period; of these six reviews, five[13,14,17–19] reported on multidimensional considerations (eg, safety, adherence to evidence-based practice standards, diet allergies), informing the use of GFCF diets in the treatment of ASD.

Of the ten reviews, two[9,12] limited their review to RCTs. remaining reviews included uncontrolled studies, group descriptive/observational studies, and case reports in addition to RCTs. The most rigorous review of the GFCF diet in ASD is a 2008 Cochrane Review by Millward et al.[9] They identified only two small RCTs (n=35), which rendered a meta-analysis impossible. The authors concluded that despite the evidence of high use of this diet as well as other complementary and alternative medicines, insufficient evidence exists to support its efficacy. The review of GFCF diet studies conducted by Mulloy et al[10] identified 14 reports published over the 30 years, 1977–2007. These studies greatly varied in quality and scope; most lacked adequate control measures, and sample sizes ranged from one individual to a group of 30. These authors used preestablished criteria to judge the evidence as suggestive, preponderant, or conclusive; they found no studies providing conclusive level evidence and only three studies providing preponderant level evidence. In the most recent (2014) synthesis of the literature, Marí-Bauset et al[14] reviewed a total of 32 studies of various designs published between 1971 and 2012, of which 24 reported on effectiveness of GFCF diet in the treatment of ASD and 8 reported on the safety of the diet. Despite the breadth of evidence reviewed, these authors found the evidence supporting the effectiveness and safety of GFCF diets for treatment of ASD to remain limited and weak.

Group experimental studies

A total of seven group experimental studies[4,15,20–24] testing the effect of GFCF diet in ASD were included for review, of which six were prospective studies[4,15,20–23] and one[24] a retrospective analysis of data from one[4] of the six prospective studies. Of the six prospective studies, two were double-blind RCTs.[4,15] Two studies[20,21] used a single-blind RCT design in which the parents provided the child's food, while study personnel supported them with dietary guidance. Two studies[22,23] used an uncontrolled design to investigate the effect of GF-only, CF-only, and GFCF diet conditions (three separate interventions) on children's behaviors using non-blinded assessments of specific behaviors in the three intervention groups. Of the group experimental studies included for review, only two[15,21] restricted the age span of participants to an age range spanning ≤2 years; the

remaining studies allowed study sample age ranges of up to 18 years. Additionally, only one study[20] tested an intervention that lasted longer than 3 months. Notably, this was the only study that reported statistically significant improvements in the GFCF diet group using blinded assessment. No other studies using blinded assessment found group differences for the GFCF diet. However, one study[4] did note positive anecdotal reports for some participants on the GFCF diet. Table 3 summarizes the seven group experimental studies included in our review.

Case reports

A total of five case reports[5,25–28] were reviewed and are summarized in Table 4. Of these five cases, one employed a

Table 3 Group experimental studies

Study	Design	Participant diagnoses	Number enrolled; number included in analysis; ages	Intervention; duration
Elder et al[4]	Double-blind RCT, repeated measures crossover.	ASD.	N=15 enrolled and analyzed; 2–16 years.	GFCF diet; 6 weeks.
Mageshwari and Minitha[23]	Observational description of entire study sample with dietary intervention study of subgroup.	ASD.	N=25 enrolled; n=10 descriptive analysis only, n=15 dietary intervention analysis; 3–18 years.	CF diet (group 1), GF diet (group 2), GFCF diet (group 3); 3 months.
Seung et al[24]	Retrospective/secondary analysis of 1-group prepost data from double-blind RCT.[4]	ASD.	N=13; n=13 analyzed; 2–16 years.	GFCF diet; 6 weeks.
Nazni et al[22]	Observational description of entire study sample with dietary intervention study of subgroup.	ASD.	N=50 enrolled with descriptive analysis; n=30 dietary intervention analysis; 3 to >11 years.	CF diet (group 1), GF diet (group 2), GFCF diet (group 3); 2 months.
Hyman et al[15]	Double-blind RCT.	ASD.	N=21 enrolled; n=14 included in analysis; 30–54 months.	GFCF diet with weekly double-blind snack challenges; 12 weeks.
Whiteley et al[20]	Two-stage, single-blind RCT using an adaptive design with interim analysis.	PDD (ICD-10 code F84).	N=72 started the trial; n=55 analyzed after 12 months, n=35 analyzed after 24 months; 4 years to 10 years 11 months.	GFCF diet; 24 months (control group received 12 months intervention as result of interim analysis).
Johnson et al[21]	Parallel 3-group, single-blind RCT.	ASD.	N= unreported; n=22 completed study; 3–5 years.	GFCF diet; 3 months.

quasi-experimental design. Irvin[25] utilized a ABAB (2-phase design where A1 is the baseline, B1 is the introduction of intervention, A2 is the withdrawal of intervention, and B2 is the reintroduction of intervention) reversal design and measured the frequency of problem behaviors in a controlled setting while on and off the GFCF diet. No significant reduction in problem behaviors was found while the child was on the GFCF diet as compared to a regular diet. However, the remaining four case reports described positive changes in cognitive, behavioral, and language symptoms of the children with ASD following implementation of the GFCF diet. Additionally, in these four cases,[5,26–28] parents reported positive results, such as improved language and cognitive development and satisfaction with the overall changes in their

Comparator	Diet provision/monitoring	Behavioral/developmental outcome measures	Results
Regular diet 6 weeks.	Study provided food for GFCF and non-GFCF diet.	ECOS, CARS, behavioral response frequencies	No group differences on behavioral/developmental measures. Positive anecdotal reports for subgroup.
No control group.	Parents oversaw child's diet per assigned group. Parents received diet counseling and written dietary guide books per assigned group.	Food intake and behavior ratings recorded daily by parents and collected weekly by investigator. Parents rated eye contact, socialization, attention, comprehension, speech, digestion, sleep, hyperactivity, anxiety/depression.	Statistical significance in pre- and post-intervention behavioral ratings not reported. 80% of intervention subgroup had behavioral improvements with majority improving in hyperactivity and digestion.
No control group.	Study provided food for GFCF diet.	Direct observation and frequency counts of: verbal responses to questions, verbal imitations, different words produced, total utterances.	No group differences in verbal communication variables measured pre and post 6-week intervention.
No control group.	Parents oversaw child's diet per assigned group. Parents received diet counseling and written dietary guide books per assigned group.	Food intake and behavior ratings recorded daily by parents and collected weekly by investigator. Parents rated attention span, repetitive body movements, need for sameness, tantruming, perseveration, aggression, passiveness, eye contact, socialization, attention, comprehension, speech, digestion, sleep, hyperactivity, and anxiety/compulsion.	Significant differences in pre- and post-intervention behavioral ratings.
Placebo: snacks that did not contain wheat flour or nonfat milk.	Researchers did not report who provided the GFCF diet food. Study provided snack challenges.	RFRLRS, Bristol stool scale, sleep diaries, actigraphy, Conners abbreviated rating scale, target symptoms scale.	No group differences in frequency or quality of stools, sleep, activity, attention/activity ratings. Group RFRLRS data were higher 2 hours post placebo, but not different 24 hours post challenge.
Control group continued their regular diet.	Parents oversaw the child's diet. Study nutritionists monitored participants receiving GFCF diet for dietary compliance and nutritional intake.	ADOS, GARS, VABS, ADHD-IV.	Statistically significant improvements above pre-determined threshold for subjects in the GFCF diet group warranted reassignment of control participants to the intervention group at 12 months.
Two comparison groups: healthy low-sugar diet group and omega-3 supplementation group.	Parents provided food per group assignment. Parents received prepared instructional materials regarding assigned diet, and verbal and written instruction regarding potential problems.	Mullen Scales of Early Learning AGS Edition, Child Behavior Checklist 1 1/3–5, Direct Behavior Observation Measure.	No significant gains in development for dietary intervention group. No clinically significant differences in behavioral outcomes for dietary intervention group. No group differences in behavioral outcome scores.

Abbreviations: ADHD-IV, Attention-deficit hyperactivity disorder – IV rating scale; ADOS, Autism Diagnostic Observation Schedule; AGS, American Guidance Service; ASD, autism spectrum disorder; CARS, Childhood Autism Rating Scale; CF, casein-free only; ECOS, Ecological Communication Orientation Scale; GARS, Gilliam Autism Rating Scale; GF, gluten-free only; GFCF, gluten-free, casein-free; ICD, International Classification of Diseases; PDD, pervasive developmental delay; RFRLRS, Ritvo-Freeman Real Life Rating Scale; RCT, randomized controlled trial; VABS, Vineland Adaptive Behavior Scale.

Table 4 Case reports

Study	Age; diagnosis	Previous/additional therapies	Behavioral/developmental symptoms preceding intervention	Gastrointestinal/ physiologic symptoms preceding intervention	Intervention	Behavioral outcome	Gastrointestinal outcome
Irvin[25]	12-year-old male; ASD and intellectual disability.	GCCF diet for 1 year prior to initial trial.	Extreme self-injury, physical aggression, property destruction, and self-restraint.	None reported.	Single case ABAB quasi-experimental design: A1=1 year GFCF diet, B1=12 days regular diet, A2=10 days GFCF diet, B2=30 months regular diet.	No change in problem behaviors. Behaviors measured during attention, demand, and play conditions.	None reported.
Hsu et al[28]	42-month-old male; ASD and CHARGE syndrome.	Speech, occupational, physical, and sensory integration therapy.	Delayed motor, language, concept, social comprehension, and general development. Third percentile height and weight.	Postprandial vomiting and long-term constipation.	GFCF diet was introduced and resulted in noticeable behavioral changes.	Improved eye contact after 2.5 months. Improved physiological biometry and interpersonal relations after 5 months. Improved development within 11 months.	Improved appetite, and reduced postprandial vomiting and constipation within 2.5 months.
Gannage[26]	3-year-old male; Regressive autism at 18 months old.	Previous therapies – supplements: probiotics, essential fatty acids, B vitamins. Additional therapies – behavioral therapies.	Language loss, self-stimulatory behavior, hyperactivity.	Abnormal stool color and consistency.	CAM interventions: Dietary: GFCF diet Medication: antifungal and antiviral medications. Heavy metal toxicity treatment: chelation therapy, dimercaptosuccinic acid, α-lipoic acid, zinc, selenium, vitamin C, methylsulfonylmethane, taurine, and vitamin E. Nutrition supplementation: glutathione, carnosine.	At 3 years following CAM interventions, which included GFCF diet, child had greatly improved language, toilet training, increased play interaction, lowered hyperactivity. At age 11, functions as a neurotypical child without symptoms of ASD.	Improved stool consistency, 3 months after implementation of GFCF diet.
Genuis and Bouchard[27]	5-year-old male; regressive autism diagnosed at 3 years old, language disorder, positive screen for celiac disease at 5 years old.	Speech language therapy, intensive educational programming.	Developmental delay, language and communication impairment, difficulty sleeping, depressed mood, disproportionate anger, inappropriate emotions, inability to tolerate bright lights.	Abdominal bloating/ pain, belching, nausea, vomiting, diarrhea, chronic upper respiratory infections, chronic congestion.	Gluten-restricted diet with nutritional supplementation (omega-3 and -6 fatty acids, folic acid).	After 3 months of initiating gluten-restricted diet, the child's functioning improved enough to enable enrollment in a typical classroom without an aide; the individualized learning program was no longer needed 3 months postinitiation of gluten-restricted diet.	Gastrointestinal symptoms were relieved within 1 month of initiating gluten-restricted diet.

Herbert and Buckley[5]	5-year-old female; regressive autism at 4 years old, seizure onset at puberty (12 years old).	Speech and physical therapy.	Escalating tantrums, no eye contact, lack of social awareness, hypersensitivity to sensory stimulation, hypotonia, stereotypies.	Foul-smelling orange diarrhea, abdominal distention, daily morning moaning, asthma, recurrent otitis media, recurrent sinusitis.	Parents implemented GFCF diet when the child was 5 years old. Recurrent illness treated with intravenous immunoglobulins; asthma with nutritional supplements and pharmacological supports. Treatment for inflammatory bowel disease. Experienced seizures at 12 years and did not respond to pharmacological therapy. Therefore, a ketogenic, GFCF diet was implemented.	Language improvements immediately after implementation of GFCF diet. Gradual improvement in auditory sensitivity. Gradual improvement in tantrum severity. Autism symptoms reduced over time to nonautistic range on Childhood Autism Rating Scale. Seizures were significantly improved several weeks after GFCF-ketogenic diet was implemented.	Following implementation of GFCF diet, gastrointestinal symptoms improved but did not resolve.

Note: ABAB: 2-phase design where A1 is the baseline, B1 is the introduction of intervention, A2 is the withdrawal of intervention, and B2 is the reintroduction of intervention.
Abbreviations: ASD, autism spectrum disorder; CAM, complementary and alternative medicines; CHARGE, coloboma, heart defect, atresia choanae, retarded growth and development, genital abnormality, and ear abnormality; GFCF, gluten-free, casein-free.

child. Three[5,26,27] of the five case reports noted that the GFCF diet improved the child's communication skills and cognitive scores so drastically that the children eventually no longer met the diagnostic criteria for ASD. Most notable among the five case reports reviewed was the presence of preexisting GI symptoms in the four cases,[5,26–28] reporting improvement in ASD-related symptoms after the implementation of the GFCF diet.

Group observational studies

Four group observational studies[29–32] were reviewed that contribute evidence informing more nuanced aspects of future GFCF diet trials; these studies are summarized in Table 5. An observational study by Patel and Curtis[29] incorporated pre- and posttesting of ten children who received a comprehensive, multifaceted treatment regime, which for some children included a GFCF diet. These authors reported improved behavioral, social, motor, and GI symptoms after 3–6 months. In a survey of 293 parents of children with ASD on a GFCF diet, Pennesi and Klein[30] found greatest improvements in the subgroups of children with GI symptoms, allergy symptoms, and those on the GFCF diet for longer than 6 months. In a post hoc analysis of the ScanBrit trial data, Pedersen et al[31] reported that children with the strongest probability of being a responder to GFCF diet after 12 months were those aged 7–9 years, who had clinically significant attention deficit hyperactivity disorder – IV (ADHD-IV) scores.

Discussion

Our review of the recent literature on gluten- and/or casein-restricted diets for the treatment of ASD yielded eleven reviews, seven group experimental studies, including five RCTs, five case reports, and four group observational studies published during the last 10 years (January 2005 through February 2015). As previously mentioned, the earliest reports within the literature on gluten- and/or casein-restricted diets in ASD have been case studies, with gradual movement toward more rigorous research over the last 10 years. Perhaps this review's strongest contribution to the literature informing GFCF dietary interventions in ASD is the contextual overview of the scientific literature published during the past 10 years. Of the reviews included in our study, the review conducted by Marí-Bauset et al[14] included the largest number of primary (nonreview) studies informing on the effect of gluten- and/or casein-restricted diets in the treatment of individuals with ASD (n=24). Of its 24 relevant studies, 4 (16%) were published in the 1970s, 10 (42%) were published

Table 5 Group observational studies

Study	Diagnoses	Subjects (N); GFCF diet subjects or potential responders (n); age	Design/description of the study	Measures	Results
Patel and Curtis[29]	ASD plus ADHD, Asperger syndrome plus ADHD.	N=10; number receiving GFCF diet not reported; age: 4–10 years.	Design: open label observational study. Description: 3–6 month comprehensive multidimensional treatment program including: environmental control, organic diet or organic GFCF diet if child had gluten or casein sensitivities, gastrointestinal support, antigen injection therapy, nutritional supplements, chelation therapy, injections with glutathione and methylcobamalin, and usual therapies (eg, speech therapy, occupational therapy, physical therapy, behavioral/educational therapies).	Parents, teacher, and physician pre- and postintervention reports regarding child's: motor capabilities, behavioral capabilities, educational capabilities, ASD and ADHD symptoms, and urinary metal concentration.	Improved behavior, social, motor, and GI symptoms; statistically significant reduction of urinary lead levels; four participants able to attend mainstream classes.
Harris and Card[32]	ASD.	N=13; n=7 on GFCF diet; age: 5–12 years.	Design: cross-sectional survey. Description: correlation analysis of adherence to GFCF diet to severity of gastrointestinal symptoms and behavior patterns. Group difference testing (GFCF diet vs non-GFCF diet) in number of gluten/casein containing foods consumed per week, gastrointestinal symptoms, and autism symptoms.	FFQ – adapted, GSRS, CARS.	No statistically significant relationships found between consumption of gluten- and casein-containing foods and gastrointestinal symptoms or behavior patterns. Positive anecdotal reports for improved GI symptoms and behavior patterns.
Pennesi and Klein[30]	ASD (49.4%), HFA (16.8%), AS (15.8%), PDD (4.9%), PDD-NOS (28.4%), RS (0.3%), CDD (0.3%).	N=387; n=293 on GFCF diet; age not reported.	Design: cross-sectional survey. Description: examination of group differences in degree of GFCF diet implementation, length of diet implementation, physical symptoms, (eg, gastrointestinal symptoms), and reported diet effectiveness.	A 90-question survey including inquiry of demographics, diagnoses, parental familiarity with GFCF diet, parental implementation of GFCF diet, parental report of GFCF diet effectiveness, observable changes in autism-related symptoms and autism-related behaviors	Statistically significant reduction of ASD behaviors, and physiological and social symptoms for subgroup with GI symptoms – especially constipation and diarrhea, subgroup with allergy symptoms, and subgroup of GFCF diet implementation greater than 6 months.
Pedersen et al[31]	ASD.	N=72; n=27 potential responders; age: 4–12 years.	Design: post hoc analysis of data from ScanBrit trial (Whiteley et al[20]). Description: exploration of potential explanatory variables for predicting GFCF diet responder status.	ADHD-IV total baseline score, VABS total baseline standard score, ADOS total baseline raw score, age at baseline, laboratory status, continued use of GFCF diet poststudy completion, parent evaluation of effect of dietary intervention.	Statistically significant regression analyses indicate children, aged 7–9 years, who have clinically significant ADHD-IV scores at baseline have strongest probability of benefiting from GFCF diet.

Abbreviations: ADHD, attention deficit hyperactivity disorder; ADHD-IV, ADHD rating scale IV; ADOS, Autism Diagnostic Observation Schedule; AS, Asperger's syndrome; ASD, autism spectrum disorder; CARS, Childhood Autism Rating Scale; CDD, childhood disintegrative disorder; FFQ, Food Frequency Questionnaire; GI, gastrointestinal; GFCF, gluten-free, casein-free; GSRS, Gastrointestinal Symptoms Rating Scale; HFA, high functioning autism; PDD, pervasive developmental delay; PDD-NOS, pervasive developmental delay – not otherwise specified; RS, Rett syndrome; VABS, Vineland Adaptive Behavior Scale.

in the 12-year span of 1990 and 2002, and the remaining 10 studies (42%) were published during the 7-year period of 2005 through 2012. This observation, in conjunction with the number of reviews focusing on GFCF in ASD published in 2012 and 2013 (six of ten included in our review) indicates an increased interest in GFCF treatments for ASD over the past 10 years. Researchers' collective understanding of the questions at hand has refined to reflect an incomplete but multifaceted understanding of gluten- and/or casein-restricted diets in the treatment of ASD. Some studies point to a child's age at diet introduction,[31] while others suggest duration of diet[20,30] as well as possible food sensitivities and allergies[10–12,14,18] as potential factors impacting efficacy of GFCF diet in ASD. Others note physiological abnormalities in ASD that may help to elucidate potential responders.[33–37] These findings are highly significant and similar to our conclusions about the state of the science related to the GFCF intervention in ASD.

Limitations

Findings were limited by our specific question investigating the current state of evidence regarding the use of the GFCF dietary intervention in ASD. That is, we were seeking information about results of the GFCF diet itself and not necessarily what patient characteristics might suggest the best responders. As a result, only eight studies included for review contributed evidence as to who may be the best responders to a GFCF diet for treatment of ASD.[10–12,14,18,20,30,31]

Future direction: targeting subgroups of likely responders

The recent literature indicates a need for future GFCF diet trials to target likely responders. Case report descriptions of positive effects in the four (of five) cases included in our study reporting GI symptoms are consistent with conclusions drawn from reviews published between January 2005 and February 2015. Specifically, Mulloy et al[10,11] and Marí-Bauset et al[14] recommended consideration of the GFCF diet only when food allergy and/or sensitivities have been diagnosed. In their reviews of the scientific literature, Dosman et al,[18] Hurwitz,[12] and Mari-Bauset et al[14] recommended screening for celiac disease and/or food allergies prior to implementation of the GFCF diet. Conclusions drawn in at least two reviews,[13,17] analysis of two clinical trials,[15,20] and one observational cross-sectional study[30] suggest the existence of a subgroup of responders to GFCF dietary interventions. Empirically derived information suggestive of subgroups that may be responsive to GFCF dietary interventions has only recently come to light and has not yet been incorporated into the published clinical trials included in our review.

Summary

Despite its lack of empirical validation, there is enough interest in the GFCF diet that the treatment strategy remains widely used with individuals with ASD. The GFCF diet serves as a strong exemplar of science lagging behind in its ability to inform the practices of a community of interest. Some reasons for this paucity of empirical support are discussed in the reviewed literature and include challenges related to conducting clinical trials that must ensure dietary compliance and experimental blinding in naturalistic, day-to-day settings and interactions. In short, well-controlled GFCF dietary trials are difficult to conduct but remain desperately needed in order to inform clinical treatment decisions. Further concerted efforts must be made to identify subsets of individuals (eg, those with documented GI abnormalities) who may be the best GFCF diet "responders". Finally, until such evidence is available, clinicians should advise those wishing to implement the GFCF diet that it is not likely to be a "miraculous cure" as some claim. As such, clinicians should use caution and consider a number of factors, such as the individual's overall nutritional status as well as potential added family burden related to cost and time commitments, when advising regarding implementation of the GFCF diet for individuals with ASD.

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Author contributions

JHE, CMK, and NMS contributed to the literature search. CMK, NMS, and MBD contributed to the data collection. All authors contributed toward data analysis, drafting and critically revising the paper, gave final approval of the version to be published, and agree to be accountable for all aspects of the work.

Disclosure

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