Evidence Analysis Library
Celiac Disease (2021)

Celiac Disease Systematic Review and Guideline Methods

According to the Institute of Medicine (National Academy of Sciences), "Clinical practice guidelines are statements that include recommendations intended to optimize patient care that are informed by a systematic review of evidence and an assessment of the benefits and harms of alternative care options"[1]. Clinical practice guidelines are developed by subject matter experts based on multiple factors like evidence, patient values as well as other crucial factors (such as financial cost, feasibility of implementation, or stakeholder buy-in). This section outlines and details the process and methods used to the current Evidence-based Nutrition Practice Guideline for registered dietitians working with individuals with celiac disease (CD). Methodology for this project was developed using the process from the Academy of Nutrition and Dietetics [2,3], in accordance with the Standards for Developing Clinical Practice Guidelines from the National Academy of Science using grading and guideline development tools from GRADE (Grading of Recommendations Assessment, Development and Evaluation) group.[4,5]

Overview of the Guideline Development Process

Guideline development is a detailed and comprehensive process. The steps followed to develop this guideline are below (some steps were completed concurrently):

1. Conduct an evidence scoping review to determine availability of literature;
2. Recruit an expert panel (content experts and patient advocates) that works with the evidence review team;
3. Orient the work group the 5-step systematic review process of the Academy of Nutrition and Dietetics' Evidence Analysis Center;
4. Develop research questions and a priori eligibility criteria for the systematic review;
5. Design search plan and register on PROSPERO database;
6. Medical Librarian conducts search of multiple databases;
7. Screen abstracts and full text articles based on a priori eligibility criteria;
8. Extract data and critically assess the quality of included studies (risk of bias of studies);
9. Synthesize evidence narratively (evidence summary and conclusion statements) and in table format (Study characteristics and findings table). Grade the quality of evidence for each outcome and provide GRADE tables;
10. When evidence is available, workgroup members complete GRADE's evidence-to-decision (EtD) framework to determine best recommendations based on evidence, clinical expertise and patient values.
11. When no evidence is available from the systematic review, workgroup members used these same principles (supporting evidence outside of the systematic review, clinical expertise and patient values) to develop consensus recommendations;
12. Recommendations are rated according to Academy principles and voted on and approved by workgroup members;
13. For nutrition topics outside of the scope of this guideline, the workgroup identified external evidence-based practice guidelines, and these were assessed for quality and individual recommendations voted on by workgroup members.
14. Evidence-based practice guideline is reviewed externally by nineteen individuals with content expertise using the AGREE II tool;
15. Respond to reviewer comments and update publication.

Workgroup Selection Process

To assure appropriate expertise and limit bias, the Work Group Selection sub-committee of Academy's Council on Research followed a transparent process of selecting an expert panel of subject matter experts. An open recruitment message with a link to online application was circulated via stakeholders for experts in the topic area of celiac disease. Application were reviewed by this sub-committee and six RDNs with

extensive experience in nutrition care and /or research with individuals with celiac disease. Additionally, one patient advocate, was recruited from Consumers United for Evidence-based Healthcare (CUE). This organization provides expertise in recruiting and training patient advocates. The members of the expert panel participated in all steps of systematic review process and guideline development process, described below. Academy staff and contractors supporting the expert panel included: systematic review and guideline methodologists, a medical librarian, project manager, lead analysts, and trained evidence analysts. The expert panel and evidence review team met approximately twice per month in a virtual space to develop research questions, screen studies, analyze evidence, vote on and grade conclusion statements, and develop and discuss recommendations.

Guideline Focus

Based on the results of the scoping review, it was clear that recent Evidence-based nutrition guidelines for individuals with CD do not focus on the medical nutrition therapy or guidelines to help registered dietitian nutritionist primarily working in the United States. Therefore, in this guideline, the authors focused on effectiveness of nutrition interventions like FODMAP diet, gluten-free diet, prebiotics/probiotics, oats, and supplements. For nutrition topics outside of the scope of this guideline, external evidence-based guidelines were reviewed using the AGREE II tool and individual graded recommendations were voted on by workgroup members in order to provide practitioners with a comprehensive guide to CD nutrition care (Please see Recommendation Overview Table).

Systematic Review Process

Question Development, Literature Search and Study Selection

This guideline followed the Academy of Nutrition and Dietetics systematic review methodology. During the initial teleconference calls, the expert panel developed a list of questions that were deemed important for clinicians and patients (**Table 1**). The expert panel developed the *a priori* inclusion and exclusion criteria as listed in **Table 2**. The PICO questions and search plan for this systematic review were registered a priori on the PROSPERO database (#CRD42020169998)[6]

A comprehensive search of literature was conducted by an information specialist using MEDLINE (Ovid), EMBASE (Ovid), Cochrane CENTRAL (Ovid), CINAHL (Ebsco), Web of Science, and PsycINFO search engines. Literature search was conducted to identify studies addressing nutrition intervention questions in individuals with celiac disease . Inclusion criteria included: human of all ages with celiac disease and published between 2007 and December 2016. Search terms included terms to identify relevant nutrition interventions patients (e.g. celiac, nutrition therapy, diet, dietitian, prebiotics, etc). The literature search focused on intervention questions identified 5,294 potential studies. The PRISMA diagram illustrating the study selection process are presented in **Figure 1**.

After the search was completed, studies were systematically screened based on *a priori* inclusion/ exclusion criteria. For intervention questions, randomized controlled trials, non-randomized trials and observational studies were included. The list of titles and abstracts were independently reviewed and marked for inclusion or exclusion (along with the reason) and any differences were resolved by discussion with a third reviewer. Full texts of articles meeting inclusion criteria were ordered and reviewed for inclusion. 83 studies met the inclusion criteria for Intervention questions. A list of excluded articles with reason for exclusion was also created to maintain transparency (available at Academy of Nutrition and Dietetics Evidence Analysis Center website).

Data Extraction and Study Quality Assessment

Relevant data was extracted from the included articles using a standardized online data extraction tool. Key information extracted from each study included: Authors information; year of publication; type of study design; details of intervention: type of intervention, duration of the intervention, who delivered the intervention, setting, number of centers; Participants: sample size, mean age, age range, gender, study

inclusion and exclusion criteria, comorbidities; Interventions: intervention details, comparison group details, medication use; Outcomes: reported primary and secondary outcomes, time points of reported outcomes; other details such as funding source.

All included studies were critically appraised for risk of bias. Two independent reviewers assessed the quality or studies using the Academy's online risk of bias tool, the Quality Criteria Checklist (QCC).[4] The questions of the QCC are based on quality constructs and risk of bias domains identified by the Cochrane Collaboration and the Agency for Healthcare Research ad Quality (AHRQ). Questions examine sampling bias, performance bias, detection bias, attrition bias, and reporting bias. Any discrepancies between the two reviewers were resolved by consensus or by a third reviewer.

Data Synthesis and Grading the Evidence

Descriptive synthesis of evidence was conducted for all identified outcomes for which there were included studies. Meta-analysis was considered for the RCTs examining effect of nutrition therapy on primary outcomes, but data was insufficient for meta-analysis for all PICO questions/outcomes.

After completion of the data extraction and data synthesis, systematic review results were provided in the following formats for the expert panel to review, edit, and approve: 1) Evidence summary: a narrative summary of all included trials for each identified outcome was drafted for each research question in the systematic review. A conclusion statement was developed for each proposed question /outcome. The conclusion statement is a clear, simple and to the point answer to the proposed questions.; 2) Study characteristics table: provided information regarding study characteristics, sample size, population, intervention details and quality of each included study; 3) Quality of evidence (strength of evidence): Each of the conclusion statements were assigned a GRADE (reference) to reflect the quality of studies, inconsistency of results, imprecision, indirectness of the evidence, and publication bias. Using this method, the evidence for each outcome of interest was graded as A (high), B (moderate), C (low), or D (very low). A GRADE table was generated using GradePro[7] and demonstrated how the strength of evidence (GRADE) was derived for each outcome of interest.

Guideline Development

This guideline followed the Academy's Evidence Analysis Center's process for guideline development. For each nutrition topic investigated for which evidence was available, 2-4 workgroup members completed GRADE's Evidence-to-Decision framework[8,9], which guides review of the balance of benefits and harms, certainty of evidence, outcome importance, resource use, equity, patient values, acceptability and feasibility based on available evidence and clinical expertise in order to develop recommendations. When no or very little evidence was available to answer the systematic review questions posed, workgroup members discussed if, even in the absence of included evidence, recommendations were still needed to guide practice. If so, the workgroup drafted consensus recommendations based on: clinical expertise, literature outside of the systematic review; and nutrition principles and growth goals for the general population, with specifications that all practice decisions should be individualized according to the client. All consensus recommendations were discussed and approved unanimously by the workgroup. The workgroup members drafted comprehensive recommendations for nutrition counseling and care for individuals with celiac disease. During this phase, the role of the expert panel members was to translate the available evidence into action statements that were clear, concise, and ready to be implemented by practitioners. The workgroup and staff rated recommendations based on strength of evidence/confidence in findings and clinical experience. Strong recommendations use the terminology "recommend" and "should", which means that this course of action should be applied to most people and practitioners can have confidence that implementing this recommendation has more benefit than risk. Weak recommendations use the terminology "suggest" and "may". Terminology for Fair or consensus recommendations were at the discretion of workgroup members. The GRADE method involves two major components: a rating for quality of evidence (described above) and rating the strength of recommendations. The evidence grades are reported at the end of the recommendation statements (e.g A, B, C, or D) and reflect the confidence in the estimated effects (**Table 3**).

When providing the level for the strength of the recommendation, a number of factors besides the quality of evidence are taken into consideration, including patient values and preferences, quality of evidence, benefits and harms, cost/resources to implement the recommendation, acceptability, feasibility, and health equity. In addition to Evidence-based recommendations, in certain scenarios "Consensus" statements were developed. These statements were developed when there was not enough evidence or evidence had too low of quality to write a graded recommendation, but the workgroup determined it was important to provide some guidance to patients and practitioners. These recommendations are ungraded, and usually refer to general or routine practice.

Once the full draft of recommendation statements was ready, it was reviewed and edited multiple times by all the workgroup members and the staff. The expert panel participated in a final blinded vote of recommendation statements, and a majority of votes approving the statement was necessary for each statement to be accepted into the final guideline. Each recommendation was approved unanimously by the WG members.

For nutrition topics outside of the scope of this guideline, external Evidence-based guidelines were reviewed using the AGREE II tool and individual graded recommendations were voted on by workgroup members in order to provide practitioners with a comprehensive guide to celiac disease nutrition care (see Overview of Nutrition Topics in Celiac Disease).

Draft Report with Supporting Rationale

Once the recommendation statements were developed, the work group members drafted a guideline manuscript based on the evidence and evidence to decision framework components, including: potentials risks and harms, conditions of application, costs, recommendation narrative/rationale and rationale for the recommendation rating. In these sections the work group members also cited additional references important to the respective topic, including discussion of studies published after our search dates or other systematic reviews on the topic.

Peer Review Process

These guidelines underwent a systematic peer review process. External review was conducted by XXXX experienced dietitians and XXX. The AGREE II tool (Appraisal of Guidelines for Research and Evaluation) criteria was used to assess the quality of guideline reporting. An additional external content review was conducted by the Celiac Disease Foundation in order to insure feedback from a variety of stakeholders in the CF community. Reviewer comments from all phases were collated by staff and sent to workgroup members for discussion and possible edits. Work group chairs coordinated the final revision of the guideline document based on review comments and the final guideline manuscript will be submitted for publication.

References

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Table 1. Intervention research Question List for Celiac Disease Systematic Review

Subtopic	Question
MNT	In patients with celiac disease, how does Medical Nutrition Therapy (MNT/nutrition counseling) provided by a registered dietitian or international equivalent, compared to a control, affect nutrition-related outcomes?
Prebiotics/Probiotics	In patients with celiac disease, what are the effects of prebiotics/probiotics, compared to a control, on nutrition-related outcomes?
Low FODMAP Diet	In patients with celiac disease, what are the effects of low-FODMAP (fermentable oligosaccharides, disaccharides, monosaccharides, and polyols) diet, compared to a control, on nutrition-related outcomes?
Gluten-Free Diet	In patients with celiac disease, what are the effects of gluten-free diet, compared to a control, on nutrition-related outcomes?
Oats	In patients with celiac disease, what are the effects of oats, compared to a control, on nutrition-related outcomes?
Supplements	In patients with celiac disease, what are the effects of supplements (e.g., calcium, iron, B vitamins, zinc, copper, multivitamin), compared to a control, on nutrition-related outcomes?

Table 2. **Celiac Disease Systematic Review Search Plan**

	Include	Exclude
Age	**All RQs:** Infants, children and adolescents (ages 0 – 17 years) and adults (aged 18+ years)	**All RQs:** No ages excluded
Settings	**All RQs:** Any setting	**All RQs:** No settings excluded
Health Status	**All RQs:** Patients who were diagnosed with celiac disease according to either the North American Society for Pediatric Gastroenterology, Hepatology and Nutrition (NASPGHAN) OR the 2012 ESPGHAN (European Society for Pediatric Gastroenterology, Hepatology, and Nutrition) definition	**All RQs:** Patients without, at risk for, or self-reported celiac disease
Nutrition-Related Problem or Condition	**All RQs:** Diabetes Mellitus (Type I); Osteoporosis; Infertility; Lymphoma; Irritable Bowel Syndrome; Thyroid Disease; Peripheral Neuropathy; Down Syndrome; Turner's Syndrome; Dementia; Hepatitis; Epilepsy; Graves' Disease; Cirrhosis; Psoriasis; Autism; Non-responsive CD; dermatitis herpetiformis; obesity	**All RQs:** None excluded
Interventions/ Exposures	**RQs 1-6:** Nutrition intervention including medical nutrition therapy (MNT) provided by a registered dietitian nutritionist (RQ 1), use of pre/probiotics (RQ 2), low FODMAP diet (RQ 3), gluten-free diet (RQ 4), oat consumption (RQ 5), supplements (e.g., calcium, iron, B vitamins, zinc, copper, multivitamin) (RQ 6).	**RQ 1:** A nutrition intervention not implemented by a registered dietitian nutritionist, or international equivalent. **RQs 2-6:** Other/no nutrition intervention
Comparison	**RQs 1-3, 5-6**: Placebo or no treatment (e.g., minimally active intervention, such as printed materials) **RQ 4:** Control (e.g., non-Celiac Disease patients, established recommendation/level)	**RQs 1-3, 5-6**: No placebo or active interventions **RQ 4:** No control or active interventions (e.g., GFD+ probiotics)
Outcome – Intermediate Outcomes/Biological Effects, clinical Outcomes (Timing/Follow-up)	**RQs 1-6:** • Anthropometrics/growth: Length/height-for-age, BMI • Bone health: DEXA scan • Nutrition status: CBC, CMP, iron profile, lipid, thyroid function, RBC folate, vitamin B12, vitamin D, zinc • GI Health/Symptom: CDSD, CDAT, CSI, ICDSQ, PROMIS Global Health, bloating, constipation, diarrhea, cancer, stool change (bristol stool chart) • Gluten-free diet adherence/compliance (e.g., histology, dietitian interview,	**RQs 1-6:** No results on outcomes of interest (Timing/Follow-up: none excluded, except for RQs 3,5: <3 months)

	Include	Exclude
	adherence questionnaire, anti-tissue transglutaminase (tTG) antibodies) • Mortality • Quality of Life: IGFDQ, WPAI:SHP (Timing/Follow-up: no minimum, except for RQs 3,5: ≥3 months)	
Study Designs	**RQ 1,4**: Randomized controlled trials, clinical controlled studies, observational studies (cohort, case control studies, cross-sectional) **RQs 2-3,4-6:** Randomized controlled trials, clinical controlled studies	**RQ 1,4:** Narrative reviews, case studies, case report, case series, noncomparative reviews, letters to the editor, systematic review, meta-analysis **RQs 2-3,4-6:** Narrative reviews, case studies, case report, case series, noncomparative reviews, letters to the editor, systematic review, meta-analysis, observational studies (cohort, case control studies, cross-sectional studies)
Size of Study Groups:	**All RQs:** -Clinical Controlled studies: N ≥ 10 for each study group -Observational studies: N ≥ 30	**All RQs:** -Clinical Controlled studies: N < 10 for each study group -Observational studies: N < 30
Study Drop Out Rate:	**All RQs:** ≤30%	**All RQs:** >30%
Language	**All RQs:** English language	**All RQs:** Non-English language
Year Range	**All RQs:** January 2007 – present (**Last guideline's lit review ended in January 2007, so we pick up from here per standard protocol**)	**All RQs:** Before 2007

Table 3. Quality of Evidence Grades

Grade	Definition
High (A)	We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate (B)	We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low (C)	Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect.
Very Low (D)	We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.

Source: GRADE handbook

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Figure 1. Search strategy flow diagram for literature examining the health effects of nutrition interventions on nutrition and health outcomes among those with celiac disease.