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A Literature Review Examining the Gluten-Free Diet Impact on Type 1 Diabetes and Weight Loss

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ABSTRACT

Background: Strict adherence of a gluten-free diet (GFD) has historically been recommended only for Celiac Disease (CD). However, its use has expanded to include using it as a treatment option for Type 1 Diabetes (T1DM) and as a weight loss diet strategy for the general population.

Purpose: The purpose of this creative component was to conduct a literature review to determine to what extent the GFD benefits individuals with T1DM and impacts weight loss.

Methods: An electronic literature search was conducted utilizing the Iowa State Online Library, PubMed and Google Scholar databases. Search terms used included "gluten and type 1 diabetes," "gluten and weight loss," "gluten and metabolic control," and "nutritional adequacy of the GFD." Peer-reviewed, full-text articles were included if they were published between January 2010 and October 2019. A total of 24 primary research studies were included for review. Of these 24 studies, 9 addressed gluten and T1DM and 15 addressed gluten and weight loss. Content of the studies found were appraised and given a quality rating using the Evidence Analysis process to determine the validity of their methods, results and conclusions.

Results: Of the primary studies included, 17 were rated as "positive" and 7 were rated as "neutral." Current literature shows a potential beneficial relationship between adherence to a GFD and treatment of T1DM, especially considering the genetic link between CD and T1DM. The literature search revealed the research examining the GFD on weight loss in the general population is limited; most studies examining the impact of GFD on weight have been conducted among those with CD. The GFD impact on weight among the general, healthy population is mixed. However, it has been shown to be beneficial when an individual's BMI starts in the

obese/overweight category; however, weight gain was also observed when the individual's BMI started in the underweight category.

Conclusions: The evidence regarding the utilization of the GFD for individuals genetically at risk for and/or diagnosed with T1DM and weight loss amongst the general healthy adult population was limited and therefore should be approached with caution.

STATEMENT OF PURPOSE

Given the steady prevalence of CD and the increased popularity of the GFD, there is a need for a review of literature that examines the existing research regarding the effectiveness of the GFD for conditions other than CD. The purpose of this review of literature is to gain a comprehensive understanding of the role gluten potentially has with prevention and/or treatment of those with T1DM, a genetically at-risk population. Additionally, this review of literature will also examine the legitimacy of the GFD for weight loss. If there is evidence to support a potential benefit, the information obtained from this review of literature will help guide the recommendations I provide to patients for the use of the GFD.

OUTLINE

The proposed literature review will discuss:

1. Background and significance of the GFD
2. Relationship between gluten intake and T1DM
    a. Dietary gluten exposure interventions amongst those with T1DM
    b. Association between maternal gluten exposure during pregnancy and T1DM development of the offspring
    c. Association between gluten introduction during infancy and T1DM development.
3. GFD as a weight loss/management dietary practice
    a. GFD association with:
        i. Weight management
        ii. Nutritional adequacy (e.g., vitamins, minerals)

METHODOLOGY

The research articles used for this review of literature were gathered online from the Iowa State University library, PubMed, and Google Scholar. Various search terms were used to locate peer-reviewed, full text literature in these search engines. The key search terms used included "gluten and type 1 diabetes," "gluten and weight loss," "gluten and metabolic control," and "nutritional adequacy of the GFD." The titles and abstracts of the identified articles were reviewed to determine relevance and pertinence to the review of literature. Randomized controlled trials were preferred, but were limited. Observational studies were used if the research pertained to GFD and T1DM or GFD and weight loss. The reference lists of included studies were cross-referenced to identify other potentially relevant studies. The search was restricted to studies published between January 2010 and October 2019. Table 1 displays the inclusion and exclusion search criteria.

Table 1. Inclusion and Exclusion Criteria for Review of Literature

Inclusion Criteria	**Exclusion Criteria**
Full-text articles	Articles with only abstract available
Peer-reviewed	Secondary reports
Primary research or meta-analysis	Major conflict of interest that could promote bias with results
No conflicts of interest reported	Conflicts of interests stated
Human studies	Molecular or Animal studies
Study taking place in America, Canada, Australia or Western Europe	Countries other than America, Canada, Australia or Western Europe
English publications	Non-English publications
Studies published between January 2010 and October 2019	Studies published before January 2010 or after October 2019

A total of 24 primary research articles were included in this review of literature. Each was critically appraised using the Evidence Analysis process (EAL, 2016). The "Worksheet Template" (Appendix A) was utilized from the Evidence Analysis Library (EAL) to gather methods, results and other pertinent information from each study (EAL, 2016). Once pertinent information was documented from each article, the literature was assessed for quality utilizing the EAL's "Quality Criteria Checklist" to rate each article as "positive," "neutral" or "negative" (Appendix B) (EAL, 2016). Based on the quality appraisal process, 17 studies were rated as "positive," while 7 were rated as "neutral." None of the studies meeting the inclusion criteria were awarded a "negative" rating. Appendix C provides detailed information on these 24 articles.

LITERATURE REVIEW

Background and Significance

Overview. Celiac Disease (CD) is a condition in which genetically susceptible individuals have an immune-mediated response to exposure of dietary gluten, causing damage to their small intestinal mucosa (Parzanese et al., 2017; Kelly, Bai, Liu & Leffler, 2015; Celiac Disease, 2009). Classic clinical presentation of CD is malabsorption, including symptoms of diarrhea, abdominal pain, weight loss, stunted growth, and low bone mineral density (Kelly et al., 2015). Celiac Disease is found more often in females than males, with a male-to-female ratio of 1:2.8 (Gujral, Freeman & Thomson, 2012). The current treatment for CD is a lifelong adherence to a strict gluten-free diet (GFD) (Parzanese et al., 2017; Kelly et al., 2015; Celiac Disease, 2009). If a GFD is not followed, patients are at increased risk for nutritional deficiencies, osteoporosis, non-Hodgkin's Lymphoma and gastrointestinal malignancy (Kelly et al., 2015). CD can present any time after gluten is introduced in the diet, however, most individuals are diagnosed between the ages of six and nine years old (Diagnosis of Celiac Disease, n.d.).

An individual is considered at risk for CD if they have a first-degree relative with CD or if they have other autoimmune diseases (Diagnosis of Celiac Disease, n.d.). Both of these risk factors are related to carrying the class II human leukocyte antigen (HLA) types DQ2 and/or DQ8 (Parzanese et al., 2017). Close family of those diagnosed with CD, such as parents, siblings or children will likely carry the HLA-DQ2 and/or HLA-DQ8 gene(s); however this does not guarantee CD development (Diagnosis of Celiac Disease, n.d.). While 30 - 40% of Whites carry this gene, the frequency of those diagnosed with CD is only at 3% (Kelly et al., 2015; Diagnosis of Celiac Disease, n.d.).

Carrying the HLA genotype also increases the individual's risk of other autoimmune diseases including type 1 diabetes mellitus (T1DM), autoimmune thyroid disease, autoimmune liver disease, Down syndrome, Turner syndrome, Williams syndrome, and selective immunoglobulin A (IgA) deficiency (Diagnosis of Celiac Disease, n.d.). Of these autoimmune conditions, the relationship between T1DM and CD has been the most studied (Abid, McGlone, Cardwell, McCallion, & Carson, 2011; Antvorskov, Josefsen, Engkilde, Funda & Buschard, 2014; Antvorskov et al., 2018; Frederiksen et al., 2013; Hakola et al., 2017; Haupt-Jorgensen, Holm, Josefsen & Buschard, 2018; Hummel, Pfluger, Hummel, Bonifacio & Ziegler, 2011; Lund-Blix et al., 2015; Sildorf, Fredheim, Svensson & Buschard, 2012; Svensson et al., 2016; Virtanen et al., 2010; Virtanen et al., 2011; Welander, Montgomery, Ludvigsson & Ludvigsson, 2014).

Screening and diagnosis. The number of individuals with CD, is likely higher than the numbers currently reported (Parzanese et al., 2017). The prevalence of diagnosed CD in the United States and around the world is around 1% or 1 in 133 people; however, over the last 50 years, the prevalence of CD has increased slightly (Parzanese et al., 2017; Kelly et al., 2015; Celiac Disease, 2009). This increase is largely due to significant improvements towards screening methods and awareness of asymptomatic CD (Kelly et al., 2015). The current and historical gold standard for CD diagnosis has been an intestinal biopsy (Diagnosis of Celiac Disease, n.d.). However, serological testing of the Tissue Transglutaminase IgA (tTG-IgA) antibody was discovered in the 1980's and has since been used as the first screening step when there is suspicion of CD (Kelly et al., 2015; Diagnosis of Celiac Disease, n.d.). The discovery of the tTG-IgA antibody screening has allowed simple testing on individuals who have a high genetic risk for CD and for those who could be asymptomatic (Kelly et al., 2015).

T1DM and CD. It is reported that 10% of all patients with T1DM also have a history of CD (Abid, et al., 2011; Antvorskov et al., 2014; Antvorskov et al., 2018; Frederiksen et al., 2013; Hakola et al., 2017; Haupt-Jorgensen et al., 2018; Hummel et al., 2011; Lund-Blix et al., 2015; Sildorf et al., 2012; Svensson et al., 2016; Virtanen et al., 2010; Virtanen et al., 2011; Welander et al., 2014). T1DM incidence is rising, particularly in children under the age of five years old (Antvorskov et al., 2014; Antvorskov et al.; 2018; Frederiksen et al., 2013; Haupt-Jorgensen et al., 2018; Virtanen et al., 2010; Virtanen et al., 2011; Welander et al., 2014). There was a 2.8 % increase in T1DM diagnosis between 1990 and 1999, with the anticipation that the number of children diagnosed with T1DM will double between 2005 and 2020 (Haupt-Jorgensen et al., 2018). T1DM is a multifactorial disease, with both genetic and environmental factors placing an individual at risk for disease development. Potential environmental factors affecting disease susceptibility include stress, low vitamin D levels, enteroviruses, gut microbiota and intake of cereal proteins (including gluten) and cow's milk proteins (Antvorskov et al., 2014; Haupt-Jorgensen et al., 2018). With the increase in T1DM incidence, more research exploring potential environmental factors such as infant dietary patterns, breastfeeding duration, and the presence and timing of enterovirus infections has been conducted (Welander et al., 2014).

In addition to using the GFD to prevent and/or treat T1DM, it is also promoted as a weight loss strategy (Gaesser & Angadi, 2012; Marcason, 2011). Choung et al. (2017) reported between 2009 and 2014, the overall prevalence of CD in the United States remained steady; however the number of individuals following a GFD doubled from 0.6% of the population to 1.2% (Choung et al., 2017). In addition, the gluten-free product market is expected to continually grow to a worth of $32.39 billion by 2025 with a compounded annual growth rate of 9.1% (Gluten-Free Products Market Size Worth $32.39 Billion by 2025, 2019). Many Americans

choose to follow a GFD because they believe it is healthier than a gluten-containing dietary pattern (Gaesser & Angadi, 2012; Marcason, 2011).

Although many Americans perceive a GFD to be healthier, this dietary pattern is defined as a diet without gluten, a protein found in wheat, barley and rye (Parzanese et al., 2017). Dietary habits of gluten-free followers could vary greatly. Minimally processed foods such as fruits, vegetables, nuts, seeds, lean meats, fish and dairy are all naturally gluten-free and appear in a well-balanced diet. Whereas, someone could also consume an overabundance of processed foods high in added sugar, saturated fat and excess sodium and technically fit the gluten-free qualifications.

This comprehensive review of literature critically assessed the current research to better understand: (1) the relationship between gluten and T1DM; (2) to what extent the GFD affects weight loss and maintenance; and (3) to determine if following the GFD without a medical indication presents any nutritional consequences.

Gluten intake and T1DM

Ten original research articles were included for analysis on the relationship between gluten intake and T1DM (Abid et al., 2011; Antvorskov et al., 2018; Frederiksen et al., 2013; Hakola et al., 2017; Hummel et al., 2011; Lund-Blix et al., 2015; Svensson et al., 2016; Virtanen et al., 2010; Virtanen et al., 2011; Welander et al., 2014). Of these 10 articles, 7 were observational cohort studies (Antvorskov et al., 2018; Frederiksen et al., 2013; Hakola et al., 2017; Lund-Blix et al., 2015; Virtanen et al., 2010; Virtanen et al., 2011; Welander et al., 2014), 1 was an observational case-controlled study (Svensson et al., 2016), 1 was a longitudinal study (Abid et al., 2011) and 1 was a randomized controlled trial (RCT) (Hummel et al., 2011). Of

these 10 articles, 7 received a “positive” quality rating (Antvorskov et al., 2018; Hakola et al., 2017; Hummel et al., 2011; Lund-Blix et al., 2015; Svensson et al., 2016; Virtanen et al., 2010). The remaining 3 articles received a “neutral” rating and were all observational cohort studies (Frederiksen et al., 2013; Virtanen et al., 2011; Welander et al., 2014).

As previously mentioned, T1DM incidence has increased quickly, at a rate much faster than can be described by a genetic drift. This observed trend has led to increased research to focus on the environmental factors that influence T1DM onset and/or progression. From the literature search previously described, there were two distinct themes related to dietary gluten exposure and T1DM. These included prenatal exposure via maternal gluten intake during pregnancy (Antvorskov et al., 2018; Virtanen et al., 2010) and infant dietary intake when solids are introduced (Abid et al., 2011; Frederiksen et al., 2013; Hakola et al., 2017; Hummel et al., 2011; Lund-Blix et al., 2015; Svensson et al., 2016; Virtanen et al., 2011; Welander et al., 2014).

The genetic link between CD and T1DM along the HLA gene has raised the interest in learning if adherence to the GFD could provide benefit to those at risk for T1DM. The relationship between GFD and T1DM has been explored amongst infants and children in the general population between birth and 15 years (Frederiksen et al., 2013; Hakola et al., 2017; Hummel et al., 2011; Lund-Blix et al., 2015; Welander et al., 2014) and children with T1DM (ages 1 - 17.7 years old) (Abid et al., 2011; Svensson et al., 2016). Although the results varied, the consensus from these 10 studies is there is no correlation between GFD and T1DM.

Six infant studies included those at increased risk for T1DM due to having an immediate relative with T1DM or expression of the HLA genotype (Frederiksen et al., 2013; Hakola et al., 2017; Hummel et al., 2011; Lund-Blix et al., 2015; Virtanen et al., 2010; Virtanen et al., 2011). These studies examined infant and maternal dietary intakes using self-report. The studies by

Virtanen et al. (2011) and Antvorskov et al. (2018) used validated food frequency questionnaires. Welander et al. (2014) and Hummel et al. (2011) utilized food diaries kept by parents. Welander et al. (2014) had parents keep intermittent food diaries, tracking only important feeding milestones such as the date of cessation of breastfeeding or the age at gluten introduction for the first year of life (researchers started with 17,055 eligible subjects, 7,206 were lost to follow-up). Whereas Hummel et al. (2011) requested parents keep a daily food record for the first 1.5 years of life (started with 150 eligible subjects, 30 were lost to follow-up). These diaries were used to assure adherence to the intervention or control group in the RCT (Hummel et al., 2011) and to document breastfeeding behaviors and gluten exposures in infancy (Welander et al., 2014). Finally, for the remaining four studies, parents answered various questions from researchers regarding infant intake (Frederiksen et al., 2013; Hakola et al., 2017; Lund-Blix et al., 2015; Virtanen et al., 2011). These questions were asked in-person, over the phone and in writing. Behavior-related questions included breastfeeding, formula feeding and solid food intake, including what kind and the age at introduction. Lund-Blix et al. (2015) required parents to keep records of breastfeeding frequency and food intake during the year of follow-up in addition to answering interview questions. This was done to assure all information was accounted for and ensured researchers would include all pertinent information in the event a parent-provided record contained information valuable to the study that would not otherwise be reported by answering a standardized question. Svensson et al. (2016) asked parents how well they thought they were following the GFD without any follow-up to support the reported dietary behavior.

Breastfeeding is reported to be beneficial in delaying the development of T1DM amongst genetically at-risk infants (Lund-Blix et al., 2015). Given this association with breastfeeding of infants at high risk for T1DM, Frederiksen et al. (2013) assessed the protective factors of

breastfeeding while introducing gluten in an infant's diet and found it to be protective against T1DM development (n=53, HR 0.47, 95% CI: 0.26-0.86, p=0.01). Neither Lund-Blix et al (2015) or Frederiksen et al. (2013) considered overall maternal dietary intake while breastfeeding, but they did control for confounding factors such as family history of T1DM, maternal education level and other perinatal factors such as delivery type, birth weight and exposure to maternal smoking during pregnancy. Gluten exposure during infancy has been shown not to be associated with any significant protection against islet cell autoimmunity progression or T1DM development (Frederiksen et al., 2013; Hakola et al., 2017; Hummel et al., 2011; Lund-Blix et al., 2015; Virtanen et al., 2011; Welander et al., 2014). In fact, Frederiksen et al. (2013) and Virtanen et al. (2011) reported early food introduction, even those without gluten (< 4 month and ≥ 6 months respectively), had a higher association with T1DM development (HR 1.91, 95% CI: 1.04 – 3.51, p = 0.04 and HR 1.75, 95% CI: 1.11 – 2.75, p = 0.006, respectively). Both reported confounding variables including maternal education level (Frederiksen et al., 2013; Lund-Blix et al., 2015). However, neither controlled for socioeconomic status, which may have impacted the dietary intakes of the mothers and infant feeding practices (Frederiksen et al., 2013; Lund-Blix et al., 2015). In the U.S., the American Academy of Pediatrics (AAP) recommends exclusive breastfeeding or formula feeding until the age of 6 months (Infant Food and Feeding, 2019). This raises the question, were the findings reported by Frederiksen et al. (2013) a representation of the general introduction of foods too early or the types of food (gluten-free or not) that lead to the findings associating with early food introduction with increased T1DM risk?

Since many of these studies were observational studies, the study subjects did not receive any kind of training or counseling on dietary intake, with the exception of two studies. The RCT,

by Hummel et al. (2011) had families meet with a nutritionist to confirm understanding of a GFD. These study participants were given a specific timeframe in which gluten introduction was appropriate (6 months [control group] or 12 months [late exposure group]) (Hummel et al., 2011). Similarly, Svensson et al., (2016) provided families with GFD dietary counseling at the beginning of the study, during which time they were instructed to follow the GFD if and when they received a T1DM diagnosis.

Welander et al. (2014), who examined gluten introduction during infection during the first year of life reported that gluten introduction during the first year was not a major risk factor for later development of T1DM (HR 0.8, 95%CI: 0.3-1.6). However, other research has reported a correlation between GFD adherence and hemoglobin A1C values. Svensson et al. (2016) reported hemoglobin A1C values decreased 21% ($p<0.001$) among those newly diagnosed with T1DM when adhering to the GFD for 12 months. In addition, Abid et al. (2011) examined short-term clinical and metabolic effects amongst children (ages 1.1 – 13.2 years) with confirmed both CD and T1DM diagnoses and found that those who adhered to a GFD had fewer severe hypoglycemic episodes. However, insulin needs also increased ($p<0.005$) (Abid et al., 2011). This increase in insulin requirement is noteworthy because it indicates higher blood glucose trends. It was not reported if these higher blood glucose values were in response to the GFD; if yes, it would explain the result of fewer hypoglycemic episodes.

This review of literature revealed mixed results between maternal gluten exposure during pregnancy on an infant's T1DM risk. Virtanen et al. (2010) found correlations between gluten-free foods consumption and increased beta cell autoimmunity in infants including low-fat margarines ($p=0.02$), berries ($p=0.02$), and coffee ($p=0.04$). These findings were only statistically significant, however, not clinically relevant. Virtanen et al. (2010) discussed the possibility that

these results could be representative of other lifestyle characteristics increasing beta cell autoimmunity in infants. These lifestyle factors included age, smoking habits, body mass index and education level of the mother, as well as, living in a rural community (Virtanen et al., 2010). Additionally, Antvorskov et al. (2018) reported women who consumed high gluten intakes (>20 grams/day) during pregnancy were more likely to have offspring with T1DM ($p=0.016$) after controlling for maternal body mass index before pregnancy, family history of all diabetes (T1DM, T2DM, and gestational diabetes), smoking during pregnancy, parental socioeconomic status, delivery type and breastfeeding duration. These findings suggest that the types of foods consumed during pregnancy may influence T1DM diagnosis in infants who are at higher risk (Virtanen et al., 2010); however, is unlikely to have an impact amongst the majority of cases.

The observational nature of the majority of the studies examining the role the GFD has on T1DM makes it difficult to determine exactly how much gluten exposure study participants had. Antvorskov et al. (2018) was the only study reviewed that attempted to measure the amount of gluten consumed but stated how difficult estimation of gluten exposure is to calculate. Additionally, the number of participants in each of these studies varied greatly, ranging from 15 (Svensson et al., 2016) to 67,565 (Antvorskov et al., 2018). Furthermore, it is important to note that these studies have only reported associations, and do not reflect cause and effect. Causation requires manipulation of one variable and measurement of directly caused changes in the other. This can be observed in a controlled experiment, such as a RCT. When discussing T1DM onset and/or progression, it is impossible to narrow down specific variables that would *cause* disease outcomes when it is possible other factors could contribute. Based on this review, it appears that gluten intake does not influence T1DM prevention or treatment amongst high risk groups.

GFD as a Weight Loss/Management Dietary Practice

The growth of the gluten-free market in the grocery industry despite a stable CD diagnosis rate suggests consumers are interested in gluten-free products even without having a medical indication. Many consumers report adhering to the GFD because they believe it to be a healthier option (Gaesser & Angadi, 2012; Marcason, 2011). In response, research is examining the use of the GFD as a weight management dietary practice. Since gluten is found in wheat-containing products another consideration in addition to its impact on weight management is to understand what extent does following the GFD impact the overall nutritional quality of one's diet including fiber and vitamins and minerals such as b-vitamins, iron, folate, and calcium.

Fourteen articles regarding using the GFD as a form of weight management or assessment of the nutritional adequacy were reviewed. Nine reviewed articles discussed gluten and weight management (Barone et al., 2015; Brambilla et al., 2013; Cheng, Brar, Lee & Green, 2010; Digiacomo, Tennyson, Green & Demmer, 2013; Kabbani et al., 2012; Kim et al., 2014; Newnham, Shepherd, Strauss, Hosking & Gibson, 2016; Reilly et al., 2011; Ukkola et al., 2012) while five articles discussed the overall nutritional adequacy of the GFD (Babio et al., 2017; Martin, Geisel Maresch, Krieger, & Stein, 2013; Miranda, Lasa, Bustamante, Churruca & Simon, 2014; Shepherd & Gibson, 2012; Wild, Robins, Burley, & Howdle, 2010). Seven of the gluten and weight management studies were rated as "positive" and consisted of cohorts and case-controlled designs (Barone et al., 2015; Brambilla et al., 2013; Cheng et al., 2010; Kabbani et al., 2012; Newnham et al., 2016; Reilly et al., 2011; Ukkola et al., 2012) while two (cohort design) were rated as "neutral" (Digiacomo et al., 2013; Kim et al., 2014). Of the five articles examining the nutritional adequacy of the GFD, three were awarded a "positive" rating (Babio et al., 2017;

Miranda et al., 2014; Shepherd & Gibson, 2012), while two were rated as "neutral" (Martin et al., 2013; Wild et al., 2010).

GFD and Weight Management

The majority of the research looking at the association between the GFD and weight management has been primarily conducted in populations with CD, for whom the diet is medically indicated (Barone et al., 2015; Brambilla et al., 2013; Cheng et al., 2010; Kabbani et al., 2012; Newnham et al., 2016; Reilly et al., 2011; Ukkola et al., 2012). Nine studies were examined (Barone et al., 2015; Brambilla et al., 2013; Cheng et al., 2010; Digiacomo et al., 2013; Kabbani et al., 2012; Kim et al., 2014; Newnham et al., 2016; Reilly et al., 2011; Ukkola et al., 2012). Of these, seven were conducted amongst those with CD (Barone et al., 2015; Brambilla et al., 2013; Cheng et al., 2010; Kabbani et al., 2012; Newnham et al., 2016; Reilly et al., 2011; Ukkola et al., 2012) and two were conducted with the general population who did not have CD (Digiacomo et al., 2013; Kim et al., 2014). The studies reviewed included all ages from 13 months to 80 years (Barone et al., 2015; Brambilla et al., 2013; Cheng et al., 2010; Digiacomo et al., 2013; Kabbani et al., 2012; Kim et al., 2014; Newnham et al., 2016; Reilly et al., 2011; Ukkola et al., 2012). All studies utilized self-reported dietary intakes. The consensus of this review is that there is not enough evidence to support prescribing the GFD for weight management in the general, healthy population. However, following a GFD for those with CD is shown to be effective in helping to achieve a healthier weight either through weight loss for those who are overweight/obese or weight gain for those who are underweight.

Several of the studies provided subjects with in-person consultations with dietitians or nutritionists to assess adherence to the GFD (Cheng et al., 2010; Kabbani et al., 2012; Reilly et

al., 2011; Newnham et al., 2016; Barone et al., 2016). These consultations included education for following the GFD (Cheng et al., 2010; Newnham et al., 2016) and assessment of diet history both in-person in a personal interview (Cheng et al., 2010; Kabbani et al., 2012; Newnham et al., 2016; Reilly et al., 2011) and from a 7-day food diary (Barone et al., 2015). Cheng et al., 2010 included nutrition counseling in their appointments and while nutrition education for weight management was not included in the methods, it was addressed by the dietitian. Three studies had participants complete a self-report question using the National Health and Nutrition Education Survey (NHANES) 2009-2014 survey (Digiacomo et al., 2013; Kim et al., 2014) or the Health Behaviour and Health among the Finnish Adult Population (Ukkola et al., 2012); no additional interventions or follow-up questions were conducted (Ukkola et al., 2012; Kim et al., 2016; and Digiacomo et al., 2013).

Weight gain while adhering to the GFD for those with CD, from infants to adults, who were classified as underweight (BMI <18.5 kg/m^2 in adults and BMI-for-age <5th percentile in children) or normal weight (BMI of 18.50-24.99 kg/m^2 for adults and BMI-for-age percentile 5 – 84% in children) prior to following the GFD was reported (Barone et al., 2015; Brambilla et al., 2013; Cheng et al., 2010; Kabbani et al., 2012; Newnham et al., 2016; Reilly et al., 2011; Ukkola et al., 2012). Similarly, Kabbani et al. (2012) and Barone et al. (2016) reported adults with CD who followed the GFD experienced weight gain ($p \leq 0.002$), but this gain did not result in a new BMI classification. For this population, a significant weight gain for those classified as underweight or normal weight may be beneficial as malnutrition is common due to the malabsorption issues related to untreated CD. Contrary to these findings, several studies examining the relationship between the GFD and weight management for those with CD who were classified as overweight or obese (BMI >25.00 kg/m^2 in adults and BMI-for-age >85th

percentile in kids) reported significant weight loss (Cheng et al., 2010; Reilly et al., 2011; Ukkola et al., 2012). Reilly et al. (2011) found 75% of children (ages 1 – 20 years) with overweight/obese BMI z-scores significantly decreased their BMI (mean change in BMI z-score/month = -0.01, p=0.01) while on the GFD. Likewise, Cheng et al. (2010) and Ukkola et al. (2012) both found weight loss among the individuals classified as overweight and obese but these outcomes were not significant. Again, these findings suggest that for those who have diagnosed CD, following the GFD may help move participants toward a healthier weight range whether that is through weight gain or loss. Finally, a review of the NHANES 2009-2014 data revealed no significant relationship between following a GFD and weight classification for adults without CD (p=0.053) (Digiacomo et al., 2013; Kim et al., 2017).

Each study exploring the relationship between the GFD and weight management had several limitations. One limitation included the small to medium sample sizes utilized in 7 of the 9 studies (n=78-698 subjects) (Barone et al., 2015; Brambilla et al., 2013; Cheng et al., 2010; Kabbani et al., 2012; Newnham et al., 2016; Reilly et al., 2011; Ukkola et al., 2012). The subjects recruited for these small to medium-sized samples were also individuals with CD. Both the sample size and lack of diversity in study subjects is a limitation because it makes it difficult to generalize study results to the general population without CD.

Another limitation is the lack of dietary compliance measurement. Several studies reported adherence to the GFD, yet they did not use food diary, dietary recalls, food frequencies or other validated surveys or tools to measure intakes (Ukkola et al., 2012; Kim et al.,2016; Digiacomo et al., 2013). Even though the majority of the remaining studies included in this review utilized follow-up techniques such as dietitian/nutritionist consults and a 7-day food diary, all intakes were still self-reported and leave potential room for error.

A final limitation is the location of the studies. Four out of nine studies took place outside the U.S. This is a limitation because while the studies included in this review had a dietary pattern similar to the United States, it is not an exact replica and results may be attributable to the overall dietary and activity practices of these countries and not solely related to the GFD. The GFD has been shown to be helpful in achieving a healthy BMI in individuals with CD. However, there is not enough evidence to support the use of the GFD as a weight management tool in the general, non-CD population.

The Nutritional Implications Related to the GFD

When questioning if a GFD is a healthier dietary pattern compared to one that contains gluten, it is imperative to consider common nutritional adequacies and inadequacies of the diet. It is also important to consider how the dietary pattern of those following a GFD compares nutritionally to the average individual. This comparison between the average consumer and those following a GFD will help to determine recommendations for RDNs in their practice.

Studies included in this review assessing the nutritional adequacy of the GFD considered primarily the adequacy of the GFD followers with CD. However, Miranda et al. (2014) also studied the nutrient value of alternative gluten-free products on the market. Results across the five studies included in this section found consistent nutritional inadequacies that are noteworthy for GFD followers.

Subjects included in this nutritional adequacy analysis all had CD and ranged in ages from 10 to 80 years old (n=58-197 subjects). The dietary intakes of the subjects was collected via validated three to seven day food diaries that included weekdays and weekend days (Babio et al., 2017; Martin et al., 2013; Miranda et al., 2014; Shepherd & Gibson, 2012; Wild et al., 2010).

The study by Miranda et al. (2014) used additional dietary tracking methods, including a validated FFQ and a 24-hour diet recall administered by a trained dietitian.

Various electronic nutrition analysis software programs completed assessments of the food diaries. Each program utilized either photographic imaging to estimate portion sizing (Babio et al., 2017; Miranda et al., 2014; Wild et al., 2010) or required subjects to use household measures to record intakes (Martin et al., 2013; Shepherd & Gibson, 2012). Miranda et al. (2014) used nutrient information from national databases for analysis of intakes, while Babio et al. (2017) used nutrient information from food labels. Wild et al. (2010), Martin et al. (2013), and Shepherd & Gibson (2012) all used a combination of nutrient information from a national database including products in each respective study's grocery market and information from food manufacturers for products not found in the database.

Miranda et al. (2014) examined 206 specific gluten-free products and 289 gluten-containing equivalent products found in the Spanish market. The gluten-free products contained twice as much fat ($p=0.001$) and one-third less protein ($p<0.001$) than their gluten-containing counterparts. This is likely to help with the palatability of the product. Gluten itself is a protein and contributes significantly to the texture and structure of baked goods. When gluten is removed often fat is used as a replacement (Miranda et al., 2014).

When the dietary intakes of GFD followers were evaluated several studies identified low consumption of several nutrients including iron, folic acid, fiber, magnesium, zinc, thiamine, and calcium (Babio et al., 2017; Martin et al., 2013; Miranda et al., 2014; Shepherd & Gibson, 2012; Wild et al., 2010). While the consumption of these nutrients were observed to be low among those following a GFD, these inadequacies are also common in the general population (Micronutrient Inadequacies in the US Population: an Overview, 2019); thus may not be

attributable to the adherence of the GFD. In fact, the 2015-2020 Dietary Guidelines for Americans identified several of these nutrients as a public health concern including dietary fiber, calcium, and iron (in females ages 19 – 50 years old) (Dietary Guidelines for Americans, 2015). The Dietary Guidelines placed an emphasis on following a balanced overall dietary pattern rather than focusing on one specific nutrient in the diet, such as gluten to ensure intake of the nutrients of concern are met. Therefore, dietitians should encourage the consumption of a complete dietary pattern and educate clients on alternative, gluten-free sources of the aforementioned nutrients if they choose to follow a GFD.

Discussion/Conclusions

This literature review identified multiple primary research studies discussing the potential link between the GFD and T1DM, the role of the GFD and weight management, and the impact of the GFD on nutritional intakes. There was not enough evidence to support using the GFD as part of a T1DM treatment plan to recommend its use outside of treatment for CD. Additionally, the evidence regarding the timing and type of gluten exposure in high-risk infants didn't play a significant role in T1DM disease prevention.

The use of the GFD for weight management for the average, healthy individual is limited. The studies reviewed indicated the GFD is effective in moving those with CD toward a healthier weight either through weight gain or weight loss; however, more research is needed examining its impact on weight among the general population. In terms of potential nutrient inadequacies, the nutrients of concerns identified among those following the GFD, is not different from those common among the general population. Overall, there is not enough evidence to support the use of the GFD outside of treatment for CD. Although individuals with CD are genetically at

increased risk for T1DM, the GFD has not been shown to aid in prevention. Additionally, there is not strong enough evidence to support the use of the GFD as a weight loss strategy among the general population.

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APPENDIX A

WORKSHEET TEMPLATE

Academy of Nutrition and Dietetics
Evidence Analysis Library® Worksheet Template

Citation	
Study Design	
Class	
Quality Rating	+ (Positive) ☐ - (Negative) ☐ ⦸ (Neutral) (choose one):
Research Purpose	
Inclusion Criteria	
Exclusion Criteria	
Description of Study Protocol	Recruitment: Design: Blinding used (if applicable): Intervention (if applicable): Statistical Analysis:
Data Collection Summary	Timing of Measurements: Dependent Variables: Independent Variables: Control Variables:
Description of Actual Data Sample	Initial: (____Males ___ Females) Attrition (final N): Age: Ethnicity: Other relevant demographics: Anthropometrics: Location:
Summary of Results	Key Findings: Other Findings:
Author Conclusion	
Reviewer Comments	
Funding Source	

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APPENDIX B
QUALITY CRITERIA CHECKLIST – PRIMARY

Quality Criteria Checklist: Primary Research

Symbols Used

+ **Positive:** Indicates that the report has clearly addressed issues of inclusion/exclusion, bias, generalizability, and data collection and analysis.

-- **Negative:** Indicates that these issues have not been adequately addressed.

∅ **Neutral:** Indicates that the report is neither exceptionally strong nor exceptionally weak.

Quality Criteria Checklist: Primary Research

RELEVANCE QUESTIONS		
1.	Would implementing the studied intervention or procedure (if found successful) result in improved outcomes for the patients/clients/population group? (NA for some Epi studies)	Yes No Unclear N/A
2.	Did the authors study an outcome (dependent variable) or topic that the patients/clients/population group would care about?	Yes No Unclear N/A
3.	Is the focus of the intervention or procedure (independent variable) or topic of study a common issue of concern to dietetics practice?	Yes No Unclear N/A
4.	Is the intervention or procedure feasible? (NA for some epidemiological studies)	Yes No Unclear N/A
If the answers to all of the above relevance questions are "Yes," the report is eligible for designation with a plus (+) on the Evidence Quality Worksheet, depending on answers to the following validity questions.		
VALIDITY QUESTIONS		
1.	**Was the <u>research question</u> clearly stated?**	Yes No Unclear N/A
1.1	Was the specific intervention(s) or procedure (independent variable(s)) identified?	
1.2	Was the outcome(s) (dependent variable(s)) clearly indicated?	
1.3	Were the target population and setting specified?	
2.	**Was the <u>selection</u> of study subjects/patients free from bias?**	Yes No Unclear N/A
2.1	Were inclusion/exclusion criteria specified (e.g., risk, point in disease progression, diagnostic or prognosis criteria), and with sufficient detail and without omitting criteria critical to the study?	
2.2	Were criteria applied equally to all study groups?	
2.3	Were health, demographics, and other characteristics of subjects described?	
2.4	Were the subjects/patients a representative sample of the relevant population?	
3.	**Were <u>study groups comparable</u>?**	Yes No Unclear N/A
3.1	Was the method of assigning subjects/patients to groups described and unbiased? (Method of randomization identified if RCT)	
3.2	Were distribution of disease status, prognostic factors, and other factors (e.g., demographics) similar across study groups at baseline?	
3.3	Were concurrent controls used? (Concurrent preferred over historical controls.)	
3.4	If cohort study or cross-sectional study, were groups comparable on important confounding factors and/or were preexisting differences accounted for by using appropriate adjustments in statistical analysis?	

	3.5	If case control study, were potential confounding factors comparable for cases and controls? (If case series or trial with subjects serving as own control, this criterion is not applicable. Criterion may not be applicable in some cross-sectional studies.)	
	3.6	If diagnostic test, was there an independent blind comparison with an appropriate reference standard (e.g., "gold standard")?	
4.	**Was method of handling withdrawals described?**		Yes No Unclear N/A
	4.1	Were follow up methods described and the same for all groups?	
	4.2	Was the number, characteristics of withdrawals (i.e., dropouts, lost to follow up, attrition rate) and/or response rate (cross-sectional studies) described for each group? (Follow up goal for a strong study is 80%.)	
	4.3	Were all enrolled subjects/patients (in the original sample) accounted for?	
	4.4	Were reasons for withdrawals similar across groups?	
	4.5	If diagnostic test, was decision to perform reference test not dependent on results of test under study?	
5.	**Was blinding used to prevent introduction of bias?**		Yes No Unclear N/A
	5.1	In intervention study, were subjects, clinicians/practitioners, and investigators blinded to treatment group, as appropriate?	
	5.2	Were data collectors blinded for outcomes assessment? (If outcome is measured using an objective test, such as a lab value, this criterion is assumed to be met.)	
	5.3	In cohort study or cross-sectional study, were measurements of outcomes and risk factors blinded?	
	5.4	In case control study, was case definition explicit and case ascertainment not influenced by exposure status?	
	5.5	In diagnostic study, were test results blinded to patient history and other test results?	
6.	**Were intervention/therapeutic regimens/exposure factor or procedure and any comparison(s) described in detail? Were intervening factors described?**		Yes No Unclear N/A
	6.1	In RCT or other intervention trial, were protocols described for all regimens studied?	
	6.2	n observational study, were interventions, study settings, and clinicians/provider described?	
	6.3	Was the intensity and duration of the intervention or exposure factor sufficient to produce a meaningful effect?	
	6.4	Was the amount of exposure and, if relevant, subject/patient compliance measured?	
	6.5	Were co-interventions (e.g., ancillary treatments, other therapies) described?	
	6.6	Were extra or unplanned treatments described?	
	6.7	Was the information for 6.4, 6.5, and 6.6 assessed the same way for all groups?	
	6.8	In diagnostic study, were details of test administration and replication sufficient?	
7.	**Were outcomes clearly defined and the measurements valid and reliable?**		Yes No Unclear N/A
	7.1	Were primary and secondary endpoints described and relevant to the question?	
	7.2	Were nutrition measures appropriate to question and outcomes of concern?	
	7.3	Was the period of follow-up long enough for important outcome(s) to occur?	
	7.4	Were the observations and measurements based on standard, valid, and reliable data collection instruments/tests/procedures?	
	7.5	Was the measurement of effect at an appropriate level of precision?	
	7.6	Were other factors accounted for (measured) that could affect outcomes?	
	7.7	Were the measurements conducted consistently across groups?	
8.	**Was the statistical analysis appropriate for the study design and type of outcome indicators?**		Yes No Unclear N/A
	8.1	Were statistical analyses adequately described the results reported appropriately?	
	8.2	Were correct statistical tests used and assumptions of test not violated?	
	8.3	Were statistics reported with levels of significance and/or confidence intervals?	

	8.4 Was "intent to treat" analysis of outcomes done (and as appropriate, was there an analysis of outcomes for those maximally exposed or a dose-response analysis)? 8.5 Were adequate adjustments made for effects of confounding factors that might have affected the outcomes (e.g., multivariate analyses)? 8.6 Was clinical significance as well as statistical significance reported? 8.7 If negative findings, was a power calculation reported to address type 2 error?	
9.	**Are <u>conclusions supported by results</u> with biases and limitations taken into consideration?** 9.1 Is there a discussion of findings? 9.2 Are biases and study limitations identified and discussed?	Yes No Unclear N/A
10.	**Is bias due to study's <u>funding or sponsorship</u> unlikely?** 10.1 Were sources of funding and investigators' affiliations described? 10.2 Was there no apparent conflict of interest?	Yes No Unclear N/A
MINUS/NEGATIVE (-) *If most (six or more) of the answers to the above validity questions are "No," the report should be designated with a minus (-) symbol on the Evidence Worksheet.*		
NEUTRAL (∅) *If the answers to validity criteria questions 2, 3, 6, and 7 do not indicate that the study is exceptionally strong, the report should be designated with a neutral (∅) symbol on the Eviden* *ce Worksheet.*		
PLUS/POSITIVE (+) *If most of the answers to the above validity questions are "Yes" (including criteria 2, 3, 6, 7 and at least one additional "Yes"), the report should be designated with a plus symbol (+) on the Evidence Worksheet.*		

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APPENDIX C

OVERVIEW TABLE

Author/ Year/ Study Design	Purpose	Population	Intervention	Key Outcomes	Conclusions	Limitations
Primary Sources, Positive Quality Rating						
Hummel et al., 2011, randomized, controlled trial (parallel)	To determine if infants with a high genetic risk for islet cell autoimmunity experience a lower risk of T1DM with delayed gluten introduction.	Genetically high risk children in Germany less than two months of age, not yet exposed to dietary gluten.	Children were randomly assigned into one of two groups – gluten introduction at 6 months (control) or 12 months (intervention) of age. Daily food diaries were used to assess adherence to intervention, measure dose at first gluten exposure and determine age at introduction of other foods.	Three years after gluten exposure, children in the control and intervention groups had a 13% and 12% (P=0.6) chance of developing islet autoantibodies, respectively.	Delayed introduction of gluten into the diet of genetically high risk children is safe, but does not increase risk for islet autoimmunity.	Randomization of dietary intervention was not blinded. Many of the participants that did not adhere to their intervention were in the intervention group.
Svensson et al., 2016, observational (case-control)	To investigate if a gluten-free diet at the time of T1DM onset will provide beneficial effects on diabetes outcome.	Newly diagnosed children with T1DM (n=15), 2 years of age or older, admitted to Copenhagen University Hospital, Herlev between March 2012 and June 2013.	Children with newly diagnosed T1DM were instructed to follow a GFD. At 6 and 12 months post diagnosis, they were given a liquid mixed meal solution. Their response was measured to determine partial remission (PR). PR was defined as insulin dose-adjusted A1c </= 9 or stimulated C-peptide >300 pmol/L	Adherence to the GFD was strongest for the first 6 months. During these first 6 months, partial remission was observed in more kids on the GFD compared to the European cohort. A1c values were 21% lower (P<0.001) in the GFD cohort at 12 months of adherence to the diet.	The GFD was associated with better outcomes in newly diagnosed T1DM patients evidenced by improvements of A1c and insulin dose-adjusted A1c.	Small sample size, non-randomized design.
Hakola et al., 2018,	To study whether the	Children born at Tampere and	Parents completed questionnaires regarding	There was no association found with	There were no significant	Information on the amount of

observational (cohort)	age at introduction of complementary food or food diversity along with breastfeeding plays a role with advanced islet autoimmunity or type 1 diabetes.	Oulu University Hospitals with the HLA genotype between September 1996 and September 2004.	oral intake and breastfeeding duration. Questionnaires were collected from trained nurses at 3, 6, 12, 18, and 24 months of age. Children were then assessed for autoantibodies and T1DM up to 15 years of age.	duration of breast feeding, age at introduction of new foods, or food diversity and development of advanced islet autoimmunity and T1DM.	relationships found between infant feeding and advanced islet autoimmunity and T1DM.	food consumed at first exposure was not obtained.
Virtanen et al., 2010, observational (cohort)	To study the potential association between maternal dietary intake and advanced beta-cell autoimmunity in their offspring.	Mothers of newborn infants from Finland recruited from three hospitals all of which express the genotype for T1DM, making them high risk.	Dietary intake was self-reported post-partum via validated food frequency questionnaires. T1DM-associated antibodies in the children were measured in 3 – 12 month intervals. Antibodies measured included antibodies against islet cells (ICA), insulin, glutamate dehydroxylase, and islet antigen 2. Endpoint of the study was positive results for ICA plus one other antibody and/or diagnosis of T1DM.	Maternal intake during pregnancy of butter, low-fat margarines, berries, and coffee increased association with beta-cell autoimmunity in offspring. These findings remained statistically significant when adjusted for confounding variables.	Only weak relationships between maternal dietary intake during pregnancy and beta-cell autoimmunity were shown.	Intake was reported to doctors and nurses, not a nutrition professional.
Antvorskov et al., 2018, observational (cohort)	To determine if maternal gluten intake during pregnancy is	All women who were Danish and pregnant between January 1996 to October	Participants received a food frequency questionnaire at 25 weeks of pregnancy. Follow ups were conducted at 6 and	Average maternal gluten intake was 13.0 g/day and 0.37% (n=247) of offspring were diagnosed with	The risk of T1DM development was positively related to maternal gluten	Gluten intake is likely underestimated as it is added to items like flour,

	related to T1DM development in their offspring.	2002. Subjects had to be fluent in Danish. Women were allowed to enter the study more than once if pregnant multiple times and were recruited in first prenatal visit.	18 months postpartum to collect information on breast-feeding. Additional follow-ups were conducted when the children were 7, 11, and 14 years of age.	T1DM. Compared to offspring of mothers with the lowest gluten intake/day (<7 grams), those from mothers with the highest intake (>20 grams) were twice as likely to have T1DM at follow-up (HR 2.0). Positive correlation between maternal gluten intake and T1DM development (P=0.016).	intake during pregnancy.	bread and other foods. Information on the diet these mothers fed their infants once born is not provided and could have influenced results.
Lund-Blix et al., 2015, observational (cohort)	To investigate a potential relationship between breast-feeding duration and age at introduction of solid foods with the risk of islet autoimmunity and T1DM in a genetically at-risk population.	Genetically at-risk (expressing the HLA genotype) newborns from the general population in Norway born between 2001 and 2007.	Dietary intake was assessed via four questionnaires between 3 and 12 months of age. Parents of participants also kept records of dietary intake to determine other food intake not included in questionnaires and to gather information on breastfeeding.	Infants who were breastfed for 12 months or longer had a lower risk of T1DM development (HR 0.37). Breast-feeding for 12 months or longer was associated with lower risk of progression from islet autoimmunity progression to T1DM. The age at introduction of solid foods or breast-feeding at the time of introduction is not related to a decreased risk of islet autoimmunity or T1DM.	Breastfeeding for 12 months or longer was shown to decrease the progression of islet autoimmunity to T1DM in genetically high risk children. There were no associations with T1DM development and age at introduction of solid foods.	The primary limitation was the lower number of individuals diagnosed with T1DM. Only 25 subjects of 726 total developed T1DM. This could be a chance finding due to the study design. There could be unmeasured confounding variables present in these study results. A

						randomized controlled trial would be ideal but is arguably unethical when measuring breast-feeding durations.
Brambilla et al., 2011, observational (case-controlled)	To evaluate the changes in BMI of those with CD while on a GFD.	Patients between ages 2 – 16 years old with CD were recruited by their family pediatrician. Participants had to maintain a seronegativity in months before study to show adherence to GFD.	Patients with CD were recruited and each matched to two healthy subjects. Random matching was done by pairing gender and age. Seronegativity was assumed to be adherence to GFD. Observation of BMI changes were made while adhering to GFD between at diagnosis and current evaluation.	Observation time was a median of 4.4 years. CD patients were less frequently overweight or obese (12% vs 23.3%, $p= 0.014$) and more frequently underweight (16% vs 4.5%, $p < 0.001$) compared to their matched controls. In those with CD following a GFD, there was a decrease in the number of underweight subjects and a slight increase in the number of overweight subjects.	The number of CD patients that are underweight at diagnosis is higher than that of their healthy peers.	Retrospective design.
Cheng et al., 2010, observational (case-control)	To determine the effect a GFD has on the BMI of those with CD.	Adults ages 18 years and older with confirmed CD and with documented BMI at diagnosis. Patient has to have met with	Adherence to GFD was monitored by dietitian visits and any reports of doctor visits due to symptoms of non-adherence. Patients met with dietitian annually after first year of diagnosis. Baseline BMI	Females had lower BMI and fewer were overweight compared to national data. More males had a normal BMI and fewer were underweight compared to national data. On a GFD, 66% of those	The GFD has a beneficial effect on BMI in CD patients. Those who were underweight, gained weight. Those who were	Convenience sample.

		nutritionist within the last 6 years.	data was compared to U.S. general population data via NHANES III: from 1988 to 1994.	underweight gained weight, 54% overweight and 47% obese lost weight.	overweight, lost weight.	
Kabbani et al., 2012, observational (case-control)	To observe BMI and weight changes in those who have CD and are following a GFD.	Adults ages 18 and above with confirmed CD and following a GFD. Recruited from Celiac treatment center.	GFD adherence was confirmed by a dietitian. Baseline and follow-up information was compared to healthy population using National health Interview Survey (NHIS).	15.8% of patients on GFD went from normal or low BMI class to an overweight BMI class. 22% of patients overweight at diagnosis gained weight. Mean BMI of cohort increased from 24.0 to 24.6 ($P<0.001$).	Adherence to a GFD in those with CD caused individuals to gain weight no matter which starting BMI class they were in. Weight maintenance counseling is recommended when following a GFD.	Retrospective design. Convenience sample.
Ukkola et al., 2012, observational (case-control)	To evaluate change in BMI of those with CD after following one year of a GFD.	All subjects were 16 years old with proven CD diagnosis. CD group was compared to general population recruited from a local referral center.	Data was collected from a nationwide Finnish survey. BMI after one year of following the GFD was assessed and compared to that of the general population. Participants were newly diagnosed with CD.	69% of underweight patients gained and 18% of overweight and 42% of obese lost weight. The rest experienced no changes in BMI. Celiac group had more favorable BMI pattern than healthy population.	BMI improved in patients who followed GFD for one year.	Follow-up of one year is rather short.
Barone et al., 2016, observational (case-control)	To evaluate the influence of a long-term GFD on the nutritional status of adult patients with CD compared	Subjects for the CD group were recruited from a GI clinic in Italy. They had confirmed biopsy diagnosis of CD. Subjects	CD group continued GFD. Healthy control group continued their normal diet. Height, weight, body composition and bone mineral density was collected. Dietary intake was evaluated	82% of CD patients had a normal BMI or were overweight and 10.3% were malnourished at time of diagnosis. After adherence to GFD, subjects with a normal	GFD has positive effect on nutrition status of CD population without causing overweight or obese patients.	Study patients did follow Mediterranean diet, which isn't the best representation compared to typical western

	to healthy controls.	had been following a GFD for a median time of 24 months. Healthy controls were matched for sex, age and social status.	based on 7-day food diary at enrollment. Dietitian instructed patients on how to complete diary.	BMI showed a significant weight gain (P=0.002), but did not cross over into the overweight or obese category. CD and control group had similar BMI, fat mass, and bone mineral density. Total calorie intake between two groups were comparable but amounts of lipids and fiber intake differed (P=0.003 and P<0.0001, respectively).		diet and as it relates to this review. Small study population. Small number of underweight patients so results in this population may not be representative of all underweight patients.
Shepherd et al., 2013, observational (case-control)	To examine the nutritional adequacy of the GFD in people with CD.	This study consisted of two groups of Australians. The first group was newly diagnosed CD patients recruited from a clinic. The second group was long-term treated CD patients recruited from private practice, public hospitals	All patients assessed by a dietitian and educated on GFD, which was to be followed for life but was analyzed for the next 12 months. Dietary adherence was assessed in follow up with dietitian. Questions were asked about adhering to GFD and utilizing 7 day food log. Food logs were also assessed using Foodworks analysis software. Blood samples were taken to assess electrolytes, renal	Inadequate folate, calcium, iron and zinc intake occurred more frequently than in the overall Australian population. Thiamin and vitamin A were more common after GFD implementation. Fiber intake was inadequate for all except for diet-experienced men. Thiamin, folate, vitamin A, magnesium, calcium and iron were	Nutritional inadequacies are common in those following the GFD and could be contributed to long-term poor food choices, but also inherent deficiencies due to following a GFD. Fortification of GF foods should be considered along with micronutrient supplementation.	Behavioral changes can occur when documenting food intake – potential for undereating. Results could be difficult to generalize to other populations. For the diet-experienced group, it was a prerequisite for the study to be

		and advertisements.	function, LFTs, iron studies, serum folate, vitamin B12, zinc, vitamin D, magnesium, calcium, and phosphorous.	commonly low in women who were newly diagnosed and experienced dieters.		following the diet, therefore, they could be a higher motivated population of CD patients. For the newly diagnosed group, they received more intensive follow up after diagnosis than they normally would. This intensive follow up was due to their involvement in the study and thus they all had excellent adherence to the new diet.
Babio et al., 2017, observational (case-control)	To compare the food and nutrient intake of CD patients to nonceliac healthy controls.	Subjects ages 10 – 23 years old diagnosed with CD at a hospital in Spain and were adherent to GFD. Healthy patients were recruited in primary and secondary	Dietitian met with cases and controls to gather background information and to teach them about using 3-day food record. Same dietitian analyzed food records when turned in. Photogenic analysis was used to estimate portion sizes on food records.	CD group reported higher intake of added sugar ($P<0.001$) and total fat ($P<0.017$). Fiber intake was below recommended amounts for both groups. CD group showed lower intakes of folic acid, calcium, iron and magnesium.	CD group had more unbalanced diet compared to control. (More added sugar and total fat, inadequate intake of micronutrients)	Micronutrient levels for GF products were limited, therefore reported intakes are underestimated. No serological testing to test

		schools and were matched via age, gender and BMI to CD patients.		On a macronutrient level, the CD group ate lower amounts of starch and higher amounts of protein.		serum nutrient levels.
Miranda et al., 2014, observational (cross-sectional)	To analyze the nutritional difference between GF foods commonly consumed in Spain to their gluten-containing equivalents. Also to analyze GFD of Celiac adults.	Adult CD patients from the Basque Country in Spain.	Analysis of nutritional value of GF and gluten containing products was completed based on label packaging. Analysis of subject intake was done via a 3-day food record, a 24 hour recall and FFQ. Photographic imaging was used to determine portions.	GF breads had 1/3 less protein ($P<0.001$) and twice as much fat ($P=0.001$), primarily saturated. Pasta had similar nutrient profile as breads but also had more sodium and less fiber. Women had lower protein and higher fat intake. Men and women had lower fiber intake.	Following a GF diet could impose nutritional deficiencies if using multiple gluten alternative products.	Small sample size of products analyzed when divided into subgroups. There were significantly more women than men in this study, which could influence the fact that women had more prominent results when it came to intakes.
Newnham et al., 2016, observational (cohort)	To evaluate the effect of treatment of patients new CD with a GFD on mucosal healing, body composition, and Celiac serology followed for 5 years.	Adults ages 18 years or older who were newly diagnosed with CD and referred to a single dietetic provider.	All participants received dietary education from a dietitian. This information was refreshed after 6 weeks and again after 12 months. At 1 year and 5 year assessments, adherence to GFD was determined, peripheral blood was collected, body composition assessed, and endoscopy and biopsy were completed.	Dietary compliance was good or excellent in all but one study participant. Mucosal remission increased with time. Fat mass increased significantly over the first year in those with normal/low BMI. Lean body mass improved at the 5 year check. Bone mass increased only in those with osteopenia or	Adherence to a GFD showed improvements in intestinal healing and return of normal body compositions.	Extremely high compliance rate to diet, which could be a source of bias. Objective adherence of diet was utilized instead of subjective.

				osteoporosis after the first year.		
Reilly et al., 2011, observational (cohort)	To evaluate children with CD who are normal or overweight BMI for age at diagnosis and to determine changes that occur in their growth after following a GFD long-term.	Children with confirmed CD recruited at a clinic in the US between 2000 and 2008.	Data was obtained retrospectively through medical records. Compliance to GFD was determine via consultations with nutritionist and serological assays. Patients with normal assays within 2 years of diagnosis and who continued to have seronegativity were deemed adherent to the diet.	Mean duration of follow up was 35.6 months. 19% of patients had elevated BMI at diagnosis and 74.5% had normal BMI. 75% of individuals with elevated BMI at diagnosis decreased their BMI significantly and normalizing in 44% of the cases (P=0.01). Patients with a normal BMI at diagnosis increased their weight and 13% became overweight (P<0.01).	Children with CD could experience beneficial effects of the GFD if they are obese or overweight.	Data was obtained retrospectively.
Abid et al., 2011, observational (longitudinal)	To observe the effects of a GFD in a group of children with confirmed T1DM and CD.	Children recruited by a clinic in Ireland already presenting with T1DM and CD between November 2000 and November 2007.	Subjects followed a GFD. Data was collected on them before starting the diet and again after following the diet for 12 months. Data collected included GI symptoms, episodes of severe hypoglycemia, daily insulin requirements, height, weight, BMI, HbA1c, hemoglobin and persistence of autoantibodies.	Ten out of 11 children showed improvement in GI symptoms. Six out of 8 patients no longer had severe hypoglycemic episodes. 9 children continued to test positive for autoantibodies. There was no significant change in height, weight, BMI or HbA1c before and after adherence to the	The GFD did demonstrate some beneficial effects such as reducing GI symptoms and severe hypoglycemic episodes. Insulin increase on the GFD.	There were no matched controls to the intervention groups. Additionally, researchers did not confirm subjects were adhering to the GFD religiously.

				diet. The mean insulin requirement increased from 0.88 to 1.1 units/kg/day ($p < 0.005$).		
Primary Sources, Neutral Quality Rating						
Welander et a., 2014, observational (cohort)	To determine if children have an increased risk of T1DM after suffering an infection at the time of gluten introduction.	All children born in southeast Sweden between October 1997 and October 1999 who had parent consent. Data from 9,414 children was used.	Parents kept a diary of the date they stopped breastfeeding, the dates of introduction to gluten containing foods, and the dates of all infections during their child's first year of life. The diary was turned in when child reached one year of age. Children were 13 years old at the end of the study.	No association was found relating infant feeding practices to risk of T1DM. Infection at time of gluten introduction played no role in future risk of T1DM. The age at gluten introduction, breastfeeding duration or gluten introduction while breastfeeding did not determine future risk for T1DM.	Gluten introduction at time of infection during the first year of life is not a major risk factor for later development of T1DM.	Information was not collected for other confounding factors such as exposure to cow's milk protein, maternal obesity, maternal gestational diabetes, and maternal dietary restrictions and intolerances.
Virtanen et al., 2011, observational (cohort)	To assess whether early introduction of cow's milk, cereals, root vegetables and fruits increases the risk of expression of diabetes-associated	Newborn infants from Finland recruited from three hospitals all of which express the genotype for T1DM, making them high risk.	Diabetes-associated autoantibodies were measured at 3 – 12 month intervals. Families kept record of age at introduction of new foods and answered a questionnaire regarding this information at each visit. The endpoint was repeated positive tests for islet cell antibodies, plus	Introduction of root vegetables by 4 months old was associated with an increased risk of beta-cell autoimmunity. Introduction of cereals and egg were associated with the endpoint of the study but only for the first 3 years of life.	Early introduction of root vegetables by the age of 4 months old is associated with an increased risk of beta-cell autoimmunity in kids with high genetic risk of T1DM.	Only age at the introduction of new foods was included, not the amount of food that was consumed.

	autoantibodies.		at least one other antibody and/or T1DM.			
Frederiksen et al., 2013, observational (cohort)	To observe infant exposures, especially diet, and their association with development of T1DM.	Genetically at-risk children recruited from either a hospital or clinic in Denver, Colorado. Kids were placed into one of two groups. One group consisted of babies who were genetically tested for the HLA genotype. The other group were newborns to the age of 8 years old with one first-degree relative with T1DM.	Dietary intake data for infants was collected from mothers either over the phone or in in-person interviews every 3 months until 15 months of age. Children completed clinic visits annually. Diabetes was diagnosed by a physician and was confirmed by polyuria, polydipsia and a glucose tolerance test.	Early (<4 months of age) exposure to fruit and late (>/=6 months of age) exposure to rice/oat was associated with increased rates of T1DM. Hazard ratios of 2.23 and 2.88, respectively with 95% CI). Breastfeeding during wheat/barley introduction was found to protect against T1DM.	Introduction of new foods between the ages of 4 and 5 months appears to be safe. Breastfeeding appears to have protection effect against T1DM.	An amount of each food at each introduction was not provided. Additionally, there was no information given about who recorded or interpreted nutrition intake, such as nurses doctors or dietitians.
Digiacomo et al., 2013, observational (cohort)	To estimate the prevalence of those following the GFD without CD diagnosis and determine their demographics and general health status.	Adult participants from the NHANES survey from 2009 – 2010.	Participants responded to questionnaires about following a GFD. Lab results and body measurements were obtained.	Weighted national average of those following GFD without CD in the United States was 0.548% (about half of CD prevalence). Prevalence was higher in females than in males, which was not significant. Participants on a GFD	GFD could have positive effect on weight status. National prevalence of following GFD was 0.548%.	Results could be biased as these were people who received an annual physical, so they could be more health conscious. Other factors such as

				were more likely to be normal weight.		physical activity were not considered. Adherence to GF diet was self-reported in a yes/no question.
Kim et al., 2017, observational (cohort)	To investigate the effect of the GFD on obesity, metabolic syndrome and CVD risk in the general healthy population.	Participants of the National health and Nutrition Examination Survey (NHANES) in the United States. Years used were 2009 – 2010, 2011 – 2012, and 2013 – 2014. Subjects were 6 years old or older and did not have CD.	Dietary adherence was self-reported by answering question, "Are you on a GFD?" Blood pressure and anthropometrics were obtained. Metabolic syndrome was defined as having three of the following: abdominal obesity, high triglycerides, low HDL, high blood pressure, and high fasting blood glucose.	Weighted prevalence of GFD followers without CD was 1.3% or 3.2 million Americans. Those following a GFD were more likely to be of normal weight.	GFD may be beneficial in weight management, but does not decrease your risk of metabolic syndrome or CVD.	Potential of recall bias as adherence to GFD was patient-reported. The degree of adherence and duration of GFD was not assessed. The number of GFD followers for analysis was small.
Martin et al., 2013, observational (case-control)	To evaluate the nutritional value of the GFD and compare it to recommendations and intake of general population. Additional aim was to determine	Members of the German Celiac Society ages 8 – 17 years old. Members of this group voluntarily joined.	Participants completed a 7-day food diary which was analyzed by using DGE-PC Professional. Nutrient intake of CD patients was compared to general German population.	CD men did not have significant difference in energy intake compared to general population. Fiber intake was significantly lower in males (did not meet daily recommendation) than females. Females showed higher fat and	CD patients in Germany did have inadequate nutrient intakes on a GFD.	Relatively small sample size. Selection process of study sample hinders ability to generalize results to entire CD population. There were no lab values collected to

	portion of diet using special gluten-free products.			lower carbohydrate intake. Both males and females had lower B1, B2, B6, folic acid, magnesium and iron intake compared to healthy population.		determine serum nutrient levels.
Wild et al., 2010, observational (case-control)	To determine the nutrition composition of a GFD and compare it with a non-GFD in non-CD populations.	Adult CD patients who had followed GFD for at least 6 months. Patients were recruited by dietitian at GI clinic. Non-celiac population was from NDNS survey.	Adherence to GFD was self-reported and under review of dietitian. Dietary intake was taken by EPIC diary utilizing food pictures for portion sizes. Diaries analyzed by Microdiet version 2.52. Reference data to general population was collected via NDNS survey. Information on this survey was collected from a validated FFQ.	Females on GFD had lower intake of magnesium, iron, zinc, manganese, selenium and folate. Males had low intakes of magnesium and selenium.	Subjects following a GFD did show nutritional inadequacies in their diet. Avoidance of gluten should not be sole focus on following a GFD.	Relatively small sample size. Younger population was not well represented in comparator population.