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Treatment Regimen Adherence in Pediatric Gastroenterology

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Abstract

Objective—To review and critically evaluate the extant research pertaining to adherence in pediatric gastroenterological diseases, particularly inflammatory bowel disease and celiac disease, and to provide recommendations for future research development.

Materials and Methods—A literature search with no date restriction was conducted using PubMed and PsychInfo electronic databases and bibliographies of relevant articles.

Results—Adherence rates in inflammatory bowel disease and celiac disease range considerably from 16% to 62% and 5% to 70%, respectively, across treatments and assessment method; nonadherence frequency was generally not reported. Measures used to assess adherence included self-report, interview, diet record, and bioassay methods, and each measure demonstrated strengths and limitations. Limited evidence suggests that adherence in both disease populations is related to patient and family behavioral factors and that nonadherence is related to poor disease outcome. Treatment outcome research for nonadherence is scant in the current literature.

Conclusions—Future research should focus on refining assessment method, examining adherence and concomitant behavioral factors longitudinally, testing theoretical models of adherence, and developing efficacious treatments for nonadherence.

Keywords

Adherence; Celiac disease; Compliance; Crohn disease; Inflammatory bowel disease; Ulcerative colitis

Nonadherence to medical regimens is a significant and pervasive behavioral health issue in pediatric chronic illness management, with considerable implications for clinical decision making, morbidity and mortality, and cost-effectiveness of care (1–4). Across pediatric disease groups, the prevalence of nonadherence to prescribed medical regimens is approximately 50% in children (1,5) and 65% to 75% in adolescents (5,6). These estimates, however, have been derived primarily from nongastroenterological disease populations. Although it is plausible that the prevalence of nonadherence is comparable in gastrointestinal diseases groups, the research is not as well developed as in other populations such as people with asthma (7) and

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diabetes (8), which have been the subject of a substantial body of research focused on both measurement and treatment of nonadherence.

The treatment of gastrointestinal diseases often includes complex regimens involving multiple medications with varying dosing schedules, pill quantities, and dietary recommendations that may involve excluding a substantial amount of foods or ingredients from patients' diets. Additionally, with continued advancement of therapeutic technology expanding the variety of disease treatment options, issues pertaining to assessment and treatment of nonadherence are increasingly critical to evaluating the long-term utility and clinical outcome of medical interventions, identifying predictive factors associated with nonadherence, and reducing morbidity. Adherence assessment approaches vary depending on the target treatment (eg, medication, diet) and data source (eg, patient, parent, provider). Several methods exist, each with advantages and disadvantages; Table 1 provides a summary of these assessment approaches. Treatment of nonadherence is an area in pediatric research that is considerably underdeveloped. Current research across pediatric populations suggests that multicomponent interventions that target educational, organizational, and behavioral aspects of adherence are most promising, given that education and organizational approaches alone have generally been insufficient (1).

Much of the research on adherence to treatment regimens in gastroenterology has been conducted in adult patient populations. Unfortunately, this is of limited utility to pediatric gastroenterologists and other health care providers because disease self-management in adults does not correspond well with pediatric disease self-management. There are several potential reasons for this. First, the developmental challenges in childhood and adolescence are substantially more complex than in adulthood. Second, cognitive and behavioral patterns affecting self-management (eg, health beliefs) are likely to be more stable in adults than in children. Third, whereas adherence to treatment regimens is the responsibility of the adult patient, children and adolescents share disease management responsibility with parents or other family members, and the degree of responsibility is likely to vacillate throughout childhood. Thus, it is important to understand the unique issues pertaining to pediatric gastroenterology treatment adherence.

The purpose of this article is to provide a review and critical evaluation of the extant literature in pediatric gastroenterology that pertains to treatment regimen adherence and to provide recommendations for future investigation. Specifically, research in 2 disease groups, inflammatory bowel disease (IBD) and celiac disease (CD), is reviewed with particular attention to measurement issues and treatment of nonadherence. These diseases were chosen for review because of the potentially significant adherence issues inherent in the complex medication and/or dietary treatment regimens to which patients are required to adhere. A systematic search of the medical and psychological/behavioral literature was conducted with no date restriction, using the PubMed and PsycINFO electronic databases. Key words included *inflammatory bowel disease*, *Crohn disease*, *ulcerative colitis*, *celiac disease*, *children*, *adolescent*, *pediatric*, *adherence*, and *compliance*. Notably, a third disease group, eosinophilic disorders (eg, eosinophilic esophagitis, eosinophilic gastroenteritis), was included in the literature search but was excluded from the review because only 2 articles met the criteria for inclusion. Articles were included if the sample was exclusively pediatric (ie, younger than 21 years old), the study was empirical, adherence was assessed as part of a study or was an outcome of intervention in a treatment study, treatment was the focus of adherence (eg, procedural compliance was excluded), and the article was in English. Bibliographies of articles were also reviewed, and relevant articles meeting the inclusion criteria were included. The appendix summarizes each article included in this review.

INFLAMMATORY BOWEL DISEASE

A review of the pediatric IBD literature yielded 12 articles that met the criteria for inclusion in this review. Of those, the earlier studies generally used small sample sizes compared with more recent studies. In a case report, Milov et al (9) discussed a 14-year-old boy with nonadherence to corticosteroids assessed by serum prednisolone levels and direct observation in a hospital setting. The authors reported that after treatment by a psychologist, the patient's disease and academic functioning improved considerably. In a similar study, Delhaas et al (10) described nonadherence to corticosteroids in an 11-year-old girl that was measured via serum prednisolone and fasting levels of ACTH and cortisol and follow-up patient report in a controlled hospital setting. Nonadherence in this case was attributed to the emergence of acute anxiety and depressive symptoms during hospitalization. Despite the case report nature of these 2 studies, the results illustrate the importance of ongoing psychological/behavioral assessment in patients and families with IBD to identify and treat patients at risk for or currently exhibiting nonadherence.

Two studies by Cuffari et al (11,12) used 6-thioguanine nucleotide (6-TGN) assays (11) and (6)-TGN/6-methylmercaptopurine nucleotide (6-MMPN) assays (12) to identify suspected nonadherence and follow-up with patient report of nonadherence to immunomodulator therapy. Both studies were prospective cohort assessments using small sample sizes (N = 15 and N = 25) of adolescents. Each study reported that only 1 patient was identified as nonadherent on the basis of bioassay data and confirmation by patient report. Despite the small sample sizes, these studies offer an example of using bioassay and self-report data as complementary adherence assessments. The very low nonadherence prevalence rate reported in these 2 studies was likely a function of nonrandom sampling, inasmuch as other studies discussed here showed a higher rate. The authors indicated the potential use of 6-TGN and 6-MMPN as markers of nonadherence but urged caution in their interpretation for this purpose.

Using self-report assessment of adherence to gastrostomy tube feedings, Israel and Hassall (13) reported that 25% of adolescent patients were nonadherent to prescribed feedings. These authors examined a unique target of treatment adherence in IBD, thus providing novel adherence data. Unfortunately, the sample size of 16 limits the generalizability of the findings, and the lack of information regarding the types of questions asked of patients, training of interviewers, and reliability/validity data preclude replication of the method. Dohil et al (14) reported that 1 of 4 adolescent patients was nonadherent to recombinant human erythropoietin treatment in another study examining a novel target of treatment adherence. In addition to the small sample, frequency of nonadherence (eg, percentage of doses not taken) was not calculated, thus significantly limiting conclusions that can be drawn from this study regarding adherence to this treatment. In contrast to the small samples used in these studies, Barabino et al (15) examined 123 children via retrospective chart review. This study reported that azathioprine was discontinued in 3% of the sample because of nonadherence. Although the strengths of this study included the use of a large sample, multisite design, and examination of a commonly prescribed medication, the authors did not report the method for adherence assessment, and the retrospective design prevented more detailed data collection regarding adherence in this sample.

Recently, a few published studies have used larger sample sizes and provided more descriptive data regarding adherence assessment. For example, Mackner and Crandall (16) assessed oral medication adherence in 50 adolescents. Using both parent and patient self-report interview assessments of adherence, these authors categorized how well patients took medication into 4 levels of increasing adherence from "never" to "always." The findings of this cross-sectional study indicated that depending on the specific medication, perfect adherence ranged from 38% to 63% for parents and 43% to 75% for adolescents, which is representative of nonadherence

seen across pediatric populations. A methodological strength of this study was that the interview measure was developed on the basis of recommendations for increasing validity of self-reported adherence (1). Although the categorization of adherence offered data on the prevalence rate of nonadherence, data regarding the frequency of nonadherence could not be ascertained. The results of this study also indicated that behavioral risk factors such as family dysfunction, poor coping strategies, and patient behavioral/emotional dysfunction are associated with nonadherence to medication.

Oliva-Hemker et al (17) also examined nonadherence to medication in 51 adolescents. This cross-sectional study used pharmacy refill records to assess adherence. If medication was dispensed for 80% or more of the 180-day study period, then patients were classified as adherent. On the basis of this method, 50% and 34% of the sample were determined to be adherent to thiopurine immunomodulators and mesalamine, respectively. These authors also examined factors associated with adherence and found that number of health care visits and disease severity were greater for adherent patients. The data from the measure of adherence used in this study (ie, pharmacy refill records), however, were likely affected by the fact that some pharmacy refill scores were in excess of 100%, which may represent overdosing or recent and/or large refills close to the time of assessment. Although possible overdosing is an important adherence issue, it necessarily skews underdosing data. Unfortunately, the extent to which this occurred was unclear. Nevertheless, this study reported nonadherence rates similar to those in other studies and identified important factors related to nonadherence, including increased health care contacts and decreased disease severity, which served as protective and risk factors for nonadherence, respectively.

Another study examining thiopurine medication used 6-TGN and 6-MMPN metabolite levels in 56 children/adolescents as indicators of therapeutic response and adherence (18). This retrospective chart review study identified nonadherence as “very low” levels of both 6-TGN and 6-MMPN metabolites. By use of this definition, 16% of the sample was classified as nonadherent. The sample size in this study was larger than those of previous studies examining metabolite levels as adherence markers. Unfortunately, the findings were limited by a lack of validity checks with other measures of adherence and ambiguity regarding metabolite values considered to represent nonadherence. It is important to note that the authors acknowledged that the low prevalence rate of nonadherence observed may be a function of milder disease and better drug absorption in their sample. Thus, this study highlights the potential utility of bioassay data in adherence assessment while acknowledging some of the inherent limitations in part because of variable pharmacokinetics influenced by patient genotype, medication formulation, and effects of concurrent medications on drug metabolism.

In a study examining adherence to polymeric versus elemental formula in 98 children and adolescents, Rodrigues et al (19) found a similar rate of nonadherence in both formulas. Only 13% of elemental and 16% of polymeric formula treatments were discontinued because of nonadherence. Although this study provides important data on adherence to formula treatment adherence in IBD, inasmuch as nonadherence classification was ascertained via chart review, it is unclear how adherence was assessed. For example, patients ingesting no formula and those ingesting 50% of their formula may both have been classified as nonadherent. The study design also prevented the examination of factors that may have influenced adherence and thus could serve as targets for future intervention efforts. Nevertheless, this study provides important preliminary data regarding adherence to polymeric and elemental feeding treatments.

Stark et al (20) conducted a randomized clinical trial to test the effects of a behavioral treatment protocol to improve dietary calcium adherence in 32 children with IBD. This study compared behavioral treatment (n = 16) with an education-only (n = 16) condition using 7-day diet records for adherence assessment. Patients in the behavioral-treatment condition demonstrated

significant pretreatment–posttreatment improvement in adherence to dietary calcium intake compared with the education-only condition. Moreover, 81% of patients receiving behavioral intervention achieved their calcium intake goals regularly, compared with only 19% in the education-only condition. Although robust in design and method, this study was limited by small sample size and self-report dietary intake. Furthermore, follow-up data were not available to determine whether the observed improvement in adherence was sustained over time. Despite this, a medium effect size was observed, and the results highlight the utility of behavioral treatment for nonadherence and the use of multicomponent versus unimodal (eg, education only) interventions.

In summary, few studies in pediatric IBD have examined adherence to treatment regimens, particularly as a primary outcome. Early studies were limited by small sample sizes and/or poor adherence assessment methods, which likely contributed to the low nonadherence prevalence rates reported. More recent studies have improved methods and provide at least preliminary support for complementary methods (eg, bioassay, patient report) of adherence assessment and utility of psychological/ behavioral assessment and treatment of nonadherence. Each of these areas requires substantial development, however. Few studies reported factors associated with nonadherence, limiting conclusions that can be drawn regarding targets for intervention. Family dysfunction, patient behavioral/emotional dysfunction, poor coping strategies, health care contacts, and influence of disease severity represent areas for further investigation.

CELIAC DISEASE

A review of the pediatric CD literature yielded 21 articles that met the criteria for inclusion in this review. Inasmuch as maintenance of a gluten-free diet (GFD) is the primary treatment for CD, dietary adherence has been the subject of several investigations in pediatric CD. Similar to research in IBD, these studies have varied with respect to sample size and adherence assessment method, with considerable research focused on the role of bioassay and dietary record adherence assessment.

In a case series study examining comorbid liver cirrhosis in 5 children with CD, anti-gliadin antibodies (AGA) and anti-endomysium antibodies (EMA) were used to determine adherence to GFD (21). This study identified 2 patients as nonadherent; however, the design of this study precludes generalization of adherence findings. Also, in a cross-sectional assessment of GFD adherence in 28 children, Seyhan et al (22) reported that 35.7% of patients in the sample were nonadherent to GFD; yet, the assessment method was not documented.

Nine of the studies reviewed used a unimodal adherence assessment approach. For example, in an investigation of the long-term effects of GFD on growth and small bowel histology in 25 children, Yachha et al (23) assessed adherence via interview and EMA, although only bioassay data were reported. These data revealed a 19% rate of nonadherence. Unfortunately, the authors neglected to report data from the interview assessment, negating any comparison across measures. In addition to the small sample size, there seemed to be a selection bias, given that the selection criteria included a history of strict adherence to GFD, which would likely have significantly influenced the adherence findings. Thus, data regarding adherence to GFD from this study cannot be considered reliable. In another small study of the effect of GFD on growth, Saadah et al (24) examined 21 children with type 1 diabetes mellitus and comorbid CD. This prospective assessment used a structured telephone interview to assess adherence to GFD and categorized adherence into 4 groups: “excellent,” “good,” “fair,” and “poor.” On the basis of these classifications, approximately 80% of patients were determined to have at least “good” adherence. This study used a novel and feasible assessment approach and classified the frequency of nonadherence. Additionally, the authors accurately discussed the limitations of

serological measures as adherence markers and also the lack of a standardized measure of adherence to GFD in CD. However, adherence data were based on subjective report, and insufficient detail was provided regarding the criteria for assignment to a category. This study also classified adherence data. Although many studies across disease populations use this approach to examine differences between adherent and nonadherent patients, such classifications are arbitrary unless they are correlated with specific disease outcomes, thus limiting the generalizability of adherence data.

Selimoglu et al (25) examined serum ghrelin levels before and after the initiation of GFD in 19 children and adolescents. Nonadherence to GFD at 6-month follow-up, as measured via dietary interview by a dietitian, was reported in 10.5% of the sample. Although this study used a prospective design and a skilled dietitian for interviews, assessment reliability data were not provided, and adherence findings are limited by the small sample size and subjective nature of assessment data. In another study from the same group of researchers (26), serum nitric oxide levels before and after the initiation of GFD were used as adherence markers. This approach yielded a 17% rate of nonadherence to GFD. Although the use of nitric oxide levels to determine adherence was novel, it was not validated as an adherence measure. The use of this assay in conjunction with another validated measure of adherence would have provided data for comparison purposes. Unfortunately, the sample size was too small to enable a conclusion that nitric oxide provides a useful tool for adherence assessment. Nevertheless, this approach warrants further investigation to establish its utility.

Murphy et al (27) examined the prospective utility of lactose hydrogen breath testing to monitor mucosal healing; dietary interviews were used to assess adherence to GFD. Of 21 patients with positive breath test results, 2 were identified as nonadherent. Interestingly, the authors indicated that nonadherence was corrected with dietary advice, but no details regarding this advice or the timing of intervention or response were reported. The authors suggested that lactose hydrogen breath testing could help identify nonadherence; however, the measure of nonadherence used in this study was dietary interview. Unfortunately, given the low prevalence rate of nonadherence reported, the small sample size, and the lack of utility in older children and patients who do not demonstrate lactose malabsorption before diagnosis, lactose hydrogen breath testing does not seem to be a valid measure of adherence to GFD.

In a prospective assessment of clinical and nutritional status before and after the initiation of GFD, Patwari et al (28) used patient self-report via interview to assess dietary adherence. Of 65 children, 10.8% demonstrated nonadherence or doubtful adherence. Unfortunately, this study did not report the criteria for assignment to “doubt-ful adherence” based on assessment data. Although this study used an appropriate sample size and study design, the subjective nature and lack of descriptive data for the adherence assessment limits the generalizability of adherence findings.

Three of the studies using unimodal adherence assessment approaches examined adherence as a primary outcome. For example, Kumar et al (29) used patient self-report of diet to assess adherence to GFD in 102 adolescents. Dietary adherence was classified as strict (no gluten intake), semistrict (consuming several items of gluten per week), or normal (no gluten restriction at all). The results of this cross-sectional study indicated that 44% of the sample were nonadherent to GFD (including semistrict and normal classifications). Despite the use of a subjective measure of adherence and the lack of data on nonadherence frequency, the large sample size and specific focus on adolescents were considerable strengths of this study. Ljungman and Myrdal (30) also examined adherence to GFD in 47 adolescents in a cross-sectional study. Adherence was assessed via self-report questionnaire mailed to patients, and the findings indicated that 19% of the sample were at least moderately nonadherent to GFD. Furthermore, knowledge of CD was correlated with better adherence, and adherence was better

in girls than in boys, and in younger adolescents ages 12 to 14 years than in older adolescents ages 15 to 17 years. Additionally, patients reported more difficulty adhering to GFD in social situations compared with their home environments. Although the high adherence rates reported in this study were likely a function of social desirability bias (ie, the inclination to present oneself in a favorable manner, thus inflating adherence estimates) and of the inclusion of patients reporting gluten intake less than once per month with those reporting strict adherence, the findings indicate several factors related to adherence in this population, including knowledge, sex, age, and context of eating behavior. Each of these factors deserves further investigation to develop targeted interventions for adolescents. In another cross-sectional study using a self-report adherence assessment method, Rashid et al (31) found that 95% of 168 children and adolescents reported strict adherence to GFD. Although a small face validity assessment had been conducted on the questionnaire used in this study, reliability/validity data were not reported. Other factors that may have influenced the high reported rate of adherence include social desirability bias, lack of control over who (parent vs patient) was reporting adherence, and young age of patients in the sample (mean age 9.1 years), in whom dietary adherence was more likely a function of parent adherence. Nevertheless, this study used a large sample size and is informative with respect to patient/parent perceptions of adherence to GFD.

Seven of the studies reviewed used a multimodal adherence assessment approach. For example, Tommasini et al (32) examined the prevalence of CD and adherence to GFD in 31 children using serum tissue transglutaminase (tTG) antibodies and parent report via interview. In this prospective study, the authors stated that parent report adherence was 100%, but they mentioned that occasional nonadherence was reported in social situations. Bioassay data revealed a 28.5% rate of nonadherence after 18 months. Because it is unclear what percentage of parents reported strict adherence versus occasional nonadherence, it is difficult to evaluate the relative value of each of the adherence measures used in this study. The small sample size and lack of reliability/validity data presented for the parent report measure limited the findings. Nevertheless, this study provides preliminary support for examining tTG antibodies in relation to adherence to GFD. In another small study, Troncone et al (33) used EMA bioassay data in conjunction with 7-day diet recall to test the utility of EMA assays as indicators of slight nonadherence to GFD. In this cross-sectional study of 23 adolescents, quantities of gluten-containing foods obtained by diet recall were converted into grams by a dietitian. Only 17% of patients were classified as strictly adherent to GFD, whereas 26% consumed 0 to 0.5 g of gluten per day, 26% consumed 0.5 to 2 g of gluten per day, and 30% consumed more than 2 g of gluten per day. Moreover, only 1 of 6 patients ingesting 0 to 0.5 g of gluten per day and 3 of 6 patients ingesting 0.5 to 2 g of gluten per day had elevated EMA levels in serum. Thus, 42% of patients were identified as adherent on the basis of EMA bioassay data despite the ingestion of slight amounts of gluten each day. Although this study used a small sample of patients, the method provided a good test of the utility of EMA assay data for adherence assessment. A larger study using this method is warranted. In a similar cross-sectional study of 20 children and adolescents with type 1 diabetes mellitus and comorbid CD, Westman et al (34) used 3-day diet records, a food frequency questionnaire, and serum AGA to assess adherence to GFD. On the basis of diet records and food frequency questionnaire data, 70% of patients were classified as nonadherent to GFD, with 30% showing trace amounts of gluten in their diets and 40% showing significant amounts. AGA data were obtained via chart review and were available for only 60% of the sample; however, none of these patients demonstrated elevations in AGA, and these data were not correlated with the amount of gluten consumed according to the diet record and food frequency questionnaire data. These authors concluded that AGA data are not useful in assessing adherence. However, this conclusion is limited, given that bioassays in this study were available for only 12 of 20 patients, and they were not performed at the same time as diet records or food frequency questionnaire reporting.

Three multimodal assessment studies used 2 bioassay measures in addition to a patient report measure. Fabiani et al (35) examined adherence to GFD via self-report questionnaire and serum AGA and EMA in 23 adolescents. Of the patients in this cross-sectional study, 47.8% reported nonadherence to GFD. By contrast, only 17.4% of patients were identified as nonadherent on the basis of serological data because 19 patients had normal AGA and EMA values. Moreover, 9 of those 19, or 47.4% of those identified as normal, had reported occasional nonadherence to GFD. This study, although limited by small sample size, highlights the limitations of AGA and EMA data and the potential benefits of complementary self-report adherence assessment. Mariani et al (36) prospectively measured adherence to GFD in 47 adolescents using 3-day diet records and AGA and EMA assays. On the basis of 3-day diet records, 47% of patients demonstrated at least occasional nonadherence, and serological data identified an additional 10% of nonadherent patients. This study provides a good example of the potential utility of multimodal assessment of adherence in a moderate sample size. In a study examining the sensitivity and specificity of IgA and IgG tTG antibodies during GFD and response to dietary adherence, Bazzigaluppi et al (37) evaluated 59 children and adolescents using IgA and IgG tTG antibodies, EMA, and dietary interviews by a dietitian. Interview data were classified as “strict GFD” (perfect adherence), “occasional gluten intake” (1–2 episodes of nonadherence per month), and “frequent gluten intake” (more than 1 episode of nonadherence per week). The diet record data showed that 39% of patients reported strict adherence, 46% reported occasional nonadherence, and 15% reported frequent nonadherence, resulting in a 61% prevalence rate of nonadherence to GFD. Moreover, tTG antibodies were significantly more sensitive at identifying occasional nonadherence than were EMA data. Although no details were provided regarding the reliability and validity of the interview, the authors did classify the frequency of nonadherence using this measure. The results provide preliminary support for the complementary use of tTG antibodies and diet record data for identification of occasional nonadherence to GFD.

One multimodal assessment study also reported demographic and behavioral factors associated with adherence in CD. Anson et al (38) examined the association between parental knowledge, attitudes, and behavior and concomitant adherence to GFD in a sample of parents of 43 children. Structured interviews were conducted by nurses to identify factors associated with adherence. Physicians provided ratings of adherence based on clinical signs and symptoms, histological findings on jejunal biopsy specimens, and AGA data when available. On the basis of physician ratings, 70% of patients were classified as adherent and 28% as nonadherent, and 1 patient was not classified because of insufficient data. Patient age, sex, birth order, and number of siblings were not associated with adherence. The parents of adherent patients were more educated and had higher paternal occupational status (according to an accepted Israeli social class indicator). The parents of nonadherent patients reported more oppositional behavior and greater shared responsibility for adherence to GFD. Although this study was limited by a lack of data provided regarding the reliability and validity of the interview used, a lack of standardized behavioral measures, and potential bias of adherence estimates by provider ratings, the findings suggest the potential importance of both parental factors and child behavioral management in GFD adherence.

Only 3 studies examined the potential effects of adherence on health outcome in CD. Kolacek et al (39) examined chromosome aberrations (ie, breaks, gaps, and acentric fragments) in lymphocytes before and after the initiation of GFD in 17 children. Adherence was measured by a patient self-report questionnaire and EMA, and the results indicated that 29% and 24% of the sample were nonadherent to GFD on the basis of EMA and self-report data, respectively. Moreover, the frequency of chromosome aberrations decreased in adherent patients and remained unchanged in nonadherent patients at 24 months after the initiation of GFD. Although the small sample size limited generalizability, this study offers an example of the potential for poor outcome resulting from nonadherence to GFD. Similarly, Mora et al (40) examined the

impact of long-term GFD on bone density in a cross-sectional sample of 19 adolescents. On the basis of tTG antibodies data, 53% of the sample were classified as nonadherent. Additionally, markers of bone formation and bone resorption were significantly lower in nonadherent patients. Despite the small sample, this study also illustrates the potential negative effects of nonadherence in people with CD. Hartman et al (41) also examined bone mineral density in 41 children who were classified as either adherent or nonadherent to GFD. This study used patient and parent report of dietary adherence and also EMA and tTG assay data, resulting in 54% of the sample being classified as nonadherent. The patients determined to be nonadherent had significantly worse bone mineral density and shorter stature than did adherent patients. Although self-report of adherence was used, frequency of nonadherence was not reported. Nevertheless, these findings support those of Mora et al (40) that nonadherence to GFD is related to poorer bone health.

In summary, several studies in pediatric CD have examined adherence to treatment regimens, although few have examined adherence as a primary outcome. Many studies were limited by small sample sizes, lack of validated measures of adherence, or reporting biases, all of which contributed to variable prevalence rates of adherence reported across studies. Studies using a multimodal assessment approach provided comparisons across measures and in some cases compensated for the limitations of each measure used by identifying additional nonadherent patients. Bioassay adherence assessment data indicated that AGA and EMA may not measure adherence accurately in cases of occasional gluten ingestion but can verify significant nonadherence. By contrast, tTG assays show promise as a measure of occasional ingestion of gluten. Diet record adherence assessment also remains important, particularly with respect to quantifying gluten intake. Patient behavioral and parental factors show some evidence of being associated with nonadherence; however, this area needs further development to identify salient targets for intervention.

CONCLUSIONS

In general, research examining adherence in pediatric IBD and CD is characterized by small to moderate sample sizes and primarily retrospective chart review or cross-sectional designs with convenience samples. The treatment regimen examined in pediatric CD has primarily been adherence to GFD. By contrast, adherence in pediatric IBD has focused on various treatment regimens, although not extensively. This variability is likely a function of IBD treatment variation across patients and a lack of emphasis on adherence research in this population. Despite this, some salient findings from research in both IBD and CD have emerged from this review.

Nonadherence prevalence rates in IBD range from 16% to 66% across medications. These estimates are based on a small number of studies and vary considerably as a function of assessment method, patient age, and definition of nonadherence. There is also some evidence, albeit limited, of low nonadherence to elemental and polymeric formula feedings, impact of patient and family psychological/behavioral risk factors on nonadherence, and benefit of multicomponent behavioral treatments for nonadherence in pediatric IBD. With respect to assessment method, patient and parent self-report and interviews have been used in several studies. These measures are appealing because of their feasibility and minimal cost; however, responses can vary depending on several variables, including interview language, tone, and nonverbal behavior; interviewer reliability; and reliability/ validity of self-report questionnaires. Pharmacy records were obtained in 1 study. This is a useful noninvasive measure, but potentially inaccurate data can result from recent/large refills. Diet records were used to assess dietary adherence. These measures have been shown to be reliable in some studies and have been used across pediatric populations to examine adherence to various dietary recommendations; however, considerable variability in structure and administration and lack

of standardization limit the use of these assessment tools. 6-TGN and 6-MMPN bioassay data were also used as adherence measures in a few studies. These provide a beneficial objective measure of adherence to 6-MP/ azathioprine medication. However, factors such as pharmacokinetic variation and drug metabolism limit the use and interpretation of these assays. Although they cannot measure frequency of nonadherence by quantifying the number of doses not taken, undetectable levels of both 6-TGN and 6-MMPN can confirm suspected nonadherence.

Rates of nonadherence to GFD in pediatric CD range from 5% to 70%. Similarly to IBD, the variation in these estimates is likely a function of assessment method, patient age, and definition of nonadherence. Some evidence suggests that nonadherence is associated with poor health outcomes in CD and with limited data on the role of parental factors and behavioral management in adherence to GFD. Regarding assessment method, dietary interviews have been used in several studies. Interviews by trained clinicians are appealing because they are feasible and can be incorporated into clinic visits. As previously mentioned, however, responses to interviews and self-report questionnaires can vary depending on interpersonal and reliability/validity factors. Diet records have been used effectively in CD research, and a primary benefit of these data is that they can be used to quantify the amount of gluten intake to examine nonadherence frequency. Data on the utility of AGA and EMA bioassays are mixed, and although they may not accurately measure occasional nonadherence, they may be used to confirm suspected nonadherence in extreme cases. By contrast, tTG assays may detect occasional nonadherence to GFD.

Much of the research on adherence in pediatric IBD and CD is limited by methodological shortcomings. Research designs varied across studies, with the majority using cross-sectional or retrospective chart review assessments and almost no randomized controlled clinical trials. Furthermore, many studies did not describe the method of adherence assessment. The type of assessments used varied greatly, and several studies did not properly establish the reliability and validity of measures before their use or report reliability estimates generated from study data. Notably, reliable and valid measures of adherence are not readily available for many targets of treatment adherence assessment in these populations; thus, it is particularly important that these data be provided in studies using experimental methods to assess adherence. The definition of nonadherence also varied across studies and was not well defined in several studies. Although prevalence rates were reported for most studies, data regarding nonadherence frequency were virtually nonexistent. The majority of studies also used convenience sampling with a small number of patients/families. Consequently, many of the studies reviewed were underpowered for analysis of adherence outcomes. It should be noted, however, that the majority of studies did not examine adherence as a primary outcome but rather reported adherence rates as descriptive data or secondary outcomes. These factors likely contributed to insufficient power and various methodological approaches across these studies.

This review has identified several gaps in the extant research. Perhaps the most important of them concerns assessment methods for nonadherence prevalence rates and frequency. Several types of assessments have been used in IBD and CD research, and each has strengths and limitations. For example, self-report questionnaires, patient/parent interviews, and diet records are inexpensive and feasible to use in a busy clinic setting. Depending on the psychometric properties of these measures and how they are structured, particularly questionnaires and interviews, they have the potential to provide fairly accurate estimates of nonadherence. Furthermore, diet records can quantify frequency and identify patterns of nonadherence. The primary limitation of these measures is the reliance on subjective data with no confirmation of treatment completion (eg, ingestion of medication). In addition, they are subject to reporting biases, resulting in the potential for overestimating adherence. Pharmacy refill records are also inexpensive, although the logistics of obtaining access to them can make this a less feasible

approach to assessing adherence. This method is also subject to overestimation of adherence and, similar to subjective measures, does not confirm ingestion of medication.

Bioassays offer an objective assessment and confirmation of medication ingestion. They also seem to accurately identify significant nonadherence and are clearly useful for therapeutic drug monitoring. In addition to pharmacokinetic and drug metabolism factors, a primary limitation of bioassay assessments of adherence is that they are considerably less accurate at identifying occasional nonadherence; the possible exception may be tTG assays for GFD adherence assessment. This is a critical issue in adherence assessment, inasmuch as the findings from this review suggest that 11% (30) to 66% (16) of patients demonstrate mild to moderate nonadherence. Thus, nonadherence in this significant subpopulation of patients may go untreated if bioassays were relied on as the sole measure of treatment adherence. In addition, bioassays do not quantify frequency of nonadherence, nor can they provide data regarding the timing or patterns of treatment completion. Notably, this review indicates that virtually no research has examined patterns of nonadherence in patients. This issue is significant in understanding the frequency (ie, number of doses missed), intensity (ie, number of treatments per dose missed), and duration (ie, number of consecutive doses missed) of nonadherence in patients. Better understanding of these issues is critical for the identification of at-risk patients and the development of effective treatments for nonadherence.

Another significant gap in the current literature concerns psychological/behavioral correlates of nonadherence. This is surprising given that approximately 25% of pediatric patients with IBD meet the criteria for major depressive disorder or an anxiety disorder during the course of their illness (42). A modicum of research in IBD and CD has examined psychological/behavioral factors, and some evidence suggests that patient coping, family dysfunction, parental education, socioeconomic status, and patient behavioral/emotional dysfunction are related to adherence behavior in these 2 populations. Comprehensive understanding of these issues is needed to identify patients and families at risk for nonadherence and, alternatively, to identify protective psychological and behavioral factors that promote adherence in patients and families.

There is also a significant lack of research on treatment of nonadherence in pediatric IBD and CD, including minor interventions such as regimen simplification. One study in the CD literature (27) reported that nonadherence was “corrected,” but no details were provided regarding how this was accomplished. Another study conducted a randomized clinical trial in IBD (20) and reported significant improvements in dietary adherence via multicomponent behavioral intervention compared with education only. Thus, there are limited data on interventions to improve adherence; however, treatment outcome research, particularly randomized clinical trials, remains a significant need for both IBD and CD.

With these underdeveloped areas of research in mind, there are several issues on which future adherence research should focus. For example, research is needed to develop and rigorously test measures of adherence that can provide data regarding the frequency and patterns of nonadherence and accurately identify occasional or mild to moderate nonadherence, because these patients are potentially at risk for poorer disease outcome and further decline of disease management skills. Self-report and interview assessments require standardization because they have typically lacked sufficient reliability and validity data. Additionally, pill counts can provide an estimate of nonadherence frequency by quantifying doses not taken, and electronic monitoring can provide data regarding overall patterns of nonadherence. Thus, the utility of these measures should be examined as well. Moreover, inasmuch as no single measure of adherence can provide all essential data elements, research should examine the use of complementary assessment methods to determine what combination of measures best captures adherence behavior in these disease groups. Related to this is the need for research to

conceptualize adherence behavior on a continuum rather than as a dichotomy. Rarely are patients either 100% or 0% adherent to treatment regimens, negating a true dichotomy. Arbitrary cutoff points for classifying adherent and nonadherent patients, such as 80%, inaccurately suggest that there is a significant difference between patients who consume 80% of doses and those who consume 79%. Furthermore, unless a particular cutoff is correlated with a specific disease outcome (eg, significantly increased risk for surgery), such approaches restrict our understanding of adherence behavior in patients and families. Thus, research is needed to determine what level of adherence to specific treatments is associated with improved clinical outcomes.

Future studies should also use more rigorous research approaches such as prospective longitudinal designs to examine adherence to various treatment regimens and also psychological/behavioral factors associated with nonadherence. These studies should also test theoretical models of adherence and aim to advance our understanding of the pathways or developmental trajectories of patient and family behavioral mechanisms that affect adherence. It will be especially important to examine patterns of adherence in adolescents because this developmental period characterizes the majority of pediatric patients with IBD, and adolescents in general are likely to have poorer disease management skills. Also, treatment outcome research, particularly that which examines multicomponent treatment methods and uses randomized clinical trial designs with adherence as the primary outcome, is another critical area for further investigation because it is imperative that effective treatments for nonadherence be developed. In addition, research in other gastroenterological disease populations is needed that aims at assessing nonadherence prevalence rates and frequency, behavioral mechanisms, and treatment outcome. As previously mentioned, adherence in eosinophilic disorders represents a considerable deficit in research knowledge that warrants investigation, particularly because the recommended dietary restrictions can be especially difficult for patients and families to manage.

This review highlights several issues that have clinical implications. In general, clinicians should recognize the complexity of treatment regimen adherence, particularly in children and adolescents compared with adults, and also the patient and family psychological/behavioral factors that may influence disease management. Accurate identification and treatment of psychological/behavioral dysfunction in patients is critical to improving treatment adherence because these factors are often pervasive and preclude effective disease management. Assessment measures are available to screen for depressive and anxiety symptoms, and these can readily be incorporated into clinic visits. Equally important is assessment of family functioning and distress among family members because this also negatively affects adherence in patients. Furthermore, screening for patient/family pathological conditions may be particularly salient in adolescent patients because this is a critical developmental period during which adherence may be quite poor. Referrals to a pediatric clinical psychologist should be made upon patient/family report or recognition of significant distress or dysfunction so that those issues can be properly addressed in conjunction with treatment nonadherence.

Additionally, few patients with either IBD or CD adhere to their treatment regimens perfectly, and a considerable proportion of patients only occasionally adhere to their regimens. This is an important issue to consider with respect to assessing adherence. Given the state of the science, a complementary assessment approach involving bioassay and self-report, interview, or diet record data should be used. Although AGA and EMA assays may not be reliable measures of adherence in CD, tTG assays may confirm the ingestion of even small amounts of gluten. Such assays, combined with diet record or recall data, can provide data on frequency and patterns of nonadherence to GFD. Similarly, 6-TGN and 6-MMPN assays can be used in patients with IBD to confirm ingestion of 6-MP/azathioprine medication and verify nonadherence in extreme cases, but they cannot be used as measures of frequency of

nonadherence. Thus, a complementary approach using self-report or interview data with bioassay confirmation is preferable to determine quantity of doses consumed, patterns of dosing, and confirmation of ingestion. Clinicians should also conceptualize adherence as a continuous behavior rather than dichotomous, and acknowledge this with patients. Moreover, nonjudgmental discussion of treatment adherence should be incorporated into each clinic visit, even for consistently adherent patients, to normalize conversations about difficulties patients and families may have with following treatment recommendations. Although limited evidence regarding treatment for nonadherence exists, research across other pediatric populations suggests that multicomponent interventions involving educational, organizational, and behavior treatment approaches are essential to improving adherence in chronic illness (1). Overall, treatment teams consisting of gastroenterologists, nurses, dietitians, and psychologists should work proactively and collaboratively to monitor adherence and to intervene with patients and families as necessary.

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TABLE 1**Current assessment approaches for treatment regimen adherence**

Assessment method	Advantages	Disadvantages
Direct observation (poor feasibility)	Accurate, cost-effective, objective, measures consumption and nonadherence frequency	Feasibility, inconsistency in raters
Patient and/or parent report or interview, diet records or recall (good feasibility)	Easy, cost-effective, provides patient and/or parent perceptions of adherence behavior	Social desirability bias can overestimate adherence, subjective
Provider estimates (good feasibility)	Easy, cost-effective Objective, cost-effective	Poor reliability and validity, reactivity, subjective Feasibility, estimates potentially skewed by timing/amount of refills, does not measure consumption
Pill counts (moderate feasibility)	Easy, cost-effective, objective, fairly accurate, measures presumed consumption and nonadherence frequency	Logistical issues relying on patients bringing medications to appointments, can be manipulated positively or negatively
Electronic monitoring (moderate feasibility)	Wealth of data, objective, fairly accurate, measures presumed consumption and nonadherence frequency	Expensive, logistical issues relying on patients bringing medications to appointments, can be manipulated positively or negatively
Biological assays (good feasibility)	Blood concentration of medication, verifies consumption but not nonadherence frequency	Expensive, subject to pharmacokinetic variation and metabolism, does not measure patterns or nonadherence frequency, can be manipulated by recent dosing depending on medication

APPENDIX

Study	Sample	Research question	Study design	Adherence measures	Adherence findings	Comments
Inflammatory bowel disease Barabino et al (2002)	123 children (mean 9.8 y)	Safety and efficacy of azathioprine in IBD	Multisite retrospective chart review	Not documented	Azathioprine discontinued in 3% of sample because of nonadherence	Large multisite study; method of adherence measurement not documented; retrospective design precluded detailed information on adherence
Cuffari et al (1996)	15 adolescents (mean 13.2 y)	Comparison of erythrocyte and leukocyte DNA 6-TGN levels	Prospective cohort assessment	6-TGN and 6-MMPN levels with follow-up patient report when nonadherence was suspected	1 patient (6% of sample) had subtherapeutic 6-TGN level and reported nonadherence when confronted with pharmacy data	Small sample with low nonadherence prevalence rate reported; pharmacy adherence assessment supplied by patient report to confirm nonadherence; authors urge caution in use of 6-TGN levels as measure of adherence to 6-MP
	25 adolescents (mean 15.8 y)	6-MP metabolite levels and disease activity	Prospective cohort assessment	6-TGN and 6-MMPN levels with follow-up patient report when nonadherence was suspected	1 patient (4% of sample) had subtherapeutic 6-TGN level and reported nonadherence when confronted with pharmacy data	Small sample with low nonadherence prevalence rate reported; pharmacy adherence assessment supplied by patient report to confirm nonadherence; sample size and low nonadherence preclude use of 6-TGN levels to monitor adherence
Delhaas et al (1998)	11-year-old girl	Nonadherence to corticosteroids	Case report	Prednisolone top level, fasting serum ACTH, and cortisol levels in patient, serum cortisol levels and overnight dexamethasone suppression test in both parents, and follow-up patient report when nonadherence was suspected	Patient nonadherent to corticosteroids; disposed of oral medication and enemas via toilet	Patient was not initially suspected to be nonadherent based on psychosocial background and family functioning; however, symptoms of anxiety and depression emerged during hospitalization. Acute psychological symptoms should be recognized as risk factors for nonadherence.
Dohil et al (1998)	4 children and adolescents (mean 12 y)	Safety, efficacy, and adherence in recombinant human erythropoietin treatment	Prospective cohort assessment	Patient self-report	1 patient (25%) was determined to be nonadherent	Nonadherence frequency not quantified; small sample; nonadherent patient was 17 y and no information regarding parental monitoring obtained
Israel and Hassall (1995)	16 children (mean 13.5 y)	Safety and efficacy of prolonged G-tube enteral hyperalimentationin CD	Prospective cohort assessment	Patient self-report during clinic visits every 2 mo	25% of sample nonadherent to prescribed feedings including intermittent use (ie, ≤ 3 times/week) in 3 patients and 50%–70% adherence in 1 patient	Subjective method of adherence assessment used; no details regarding adherence assessment questions, training of interviewers, or reliability/validity; nonadherence frequency reported in 1 patient
Mackner and Crandall (2005)	50 adolescents (mean 14.7 y)	Oral medication adherence	Prospective cohort assessment	Patient and parent self-report via structured interview	38%–63% of parents and 43%–75% of patients reported perfect adherence depending on medication; 80%–91% of parents and 85%–100% of patients reported adherence most of time/always	Subjective method of adherence assessment used and adherence categorized; no mention of training/reliability of interviewer; behavior risk factors associated with nonadherence were family dysfunction, poor coping, and patient behavior/emotional dysfunction

Study	Sample	Research question	Study design	Adherence measures	Adherence findings	Comments
Milov et al (1989)	14-year-old boy	Nonadherence in corticosteroids	Case report	Serum prednisolone level and observation in hospital	After test dose of oral prednisone, no prednisolone in plasma	Observation used to supplement pharmacy studies; authors report that patient was referred to a psychologist; subsequently disease activity and academic functioning improved, and prednisone was tapered effectively
Oliva-Hemker et al (2007)	51 adolescents (mean 14.2 y)	Nonadherence to medication and identify nonadherence factors	Cross-sectional assessment	Pharmacy refill records	50% and 34% of sample classified as adherent to thiopurine immunomodulator and mesalamine, respectively; number of health care visits and disease activity were greater for adherent patients	80% cutoff used for adherence classification; prescription refill scores ranged from 0%–194%, so it is unclear whether patients were overdosing or adherence was overestimated as a result of recent and/or large refills; health care contacts may serve to protect against nonadherence; conversely, decreased disease severity may increase likelihood of nonadherence
Ooi et al (2007)	56 children and adolescents(mean 11.2 y)	Thiopurine metabolite levels and therapeutic response	Retrospective chart review	6-TGN and 6-MMPN levels	16% determined to be nonadherent based on pharmacy data (ie, “very low,” 6-TGN/6-MMPN levels)	No complementary adherence assessment used to verify pharmacy assessment; low nonadherence rate; higher 6-TGN levels may represent patients with milder disease and better absorption
Rodrigues et al (2007)	53 children and adolescents taking EF (mean 11.8 y) and 45 taking PF (mean 12.2 y)	Adherence to PF vs EF	Retrospective chart review	Chart review indicating proportion of patients completing initial 6-wk formula feeding	72% of patients taking EF and 58% of patients taking PF completed initial 6-wk course; percentage of patients discontinuing feedings because of nonadherence (not treatment failure) was 13% and 16% for EF and PF, respectively	Adherence to EF (87%) or PF (84%) is good; study design precluded examination of nonadherence frequency or factors that influenced adherence, which may serve as targets for intervention
Stark et al (2005)	32 children (16 in behavior treatment, mean 10.3 y; 16 in education only, mean 10.6 y)	Behavior treatment vs education only for improving adherence to dietary Ca intake	Multisite randomized controlled trial	7-day diet records	Baseline Ca intake was 955 mg and 945mg of Ca/day in behavior treatment and education only, respectively; all patients improved dietary adherence; behavior treatment had significantly greater Ca intake; 81% of patients in behavior treatment achieved goal of 1500mg of Ca/day; 19% of patients in education alone achieved goal; adherence to parent use of behavior skills was 92%	Findings highlight utility of behavior treatment to improve adherence to dietary regimens and provides support for multicomponent interventions compared with unimodal (eg, education only) interventions; small sample and limited to young children; self-report diet records are subject to reporting bias; rigorous method with medium effect size
Celiac disease Anson et al (1990)	Parents of 43 children (adherence mean 11.1 y, nonadherencemean 10.0 y)	Parental knowledge, attitudes, and behavior and dietary adherence to GFD	Cross-sectional assessment	Structured interviews by nurses, physician ratings, histological findings on jejunal biopsy specimen, and limited use of serum anti-gliadin antibodies	70% of patients classified as adherent, 28% as nonadherent, 1 patient not classified; patient demonstrated characteristics unrelated to adherence; parents	No mention of training/reliability of interviewer; adherence estimates potentially biased by provider ratings, but supplemented by biopsy results

Study	Sample	Research question	Study design	Adherence measures	Adherence findings	Comments
Bazzigaluppi et al (2006)	Sera of 143 children and adolescents (9 with GFD, mean 8.8 y; 64 healthy control participants, mean 6.8 y)	Sensitivity and specificity of IgA and IgG tissue-transglutaminase antibodies assay and response to GFD adherence	Retrospective longitudinal assessment	IgA and IgG tissue-transglutaminase antibodies, antiendomysium antibodies, and dietary interview by dietitian;interview classified adherence	<p>of adherent patients had more education and higher paternal occupation status; parents of nonadherent patients reported greater oppositional behavior for dietary adherence and greater shared responsibility for adherence</p> <p>39% had strict adherence; 46% occasional nonadherence; 15% frequent nonadherence. Tissue-transglutaminase antibodies significantly more sensitive at identifying occasional nonadherence compared with antiendomysium antibodies.</p>	<p>and serum assays when available; diet records not included, but could have identified patterns/frequency of nonadherence; validated behavior measures not included; study highlights role of parental factors and behavior management in adherence to GFD</p> <p>No mention of training/reliability of interviewer; dietary intake interview classified frequency of nonadherence; multimethod adherence assessment used; IgA/IgG tissue transglutaminase antibodies may be useful in determining fairly minimal nonadherence but do not identify pattern/frequency of nonadherence, suggesting utility of dietary intake interview data in clinical setting</p> <p>Serological data used to identify nonadherent patients; this assessment used in isolation precludes identification of frequency or patterns of nonadherence; small sample size</p> <p>Measure of adherence used in study was not validated as an adherence measure or used in conjunction with another adherence measure; sample size too small to conclude that serum nitric oxide levels are valid indicators of adherence</p> <p>Small sample size; self-report data used to complement serological data for adherence assessment; no data provided regarding validity/reliability of questionnaire assessment; anti-gliadin/anti-endomysial antibody assays failed to correctly identify occasional dietary nonadherence</p> <p>Nonadherence defined as even occasional, unintentional transgression from GFD</p>
Demir et al (2005)	5 children (mean 9.4 y)	Liver cirrhosis in CD	Case series	Anti-gliadin and anti-endomysium antibodies and clinical condition	2 patients (40%) nonadherent to GFD	
Ertekin et al (2005)	41 children (mean 10.4 y); adherence data on 23; 14 healthy control participants	Serum nitric oxide levels before and after GFD	Prospective assessment with healthy control group	Serum nitric oxide levels	17% of sample classified as nonadherent to GFD	
Fabiani et al (1996)	28 adolescents (mean 12.8 y), 23 with adherence data	Adherence to GFD	Cross-sectional assessment	Patient self-report questionnaire and anti-gliadin and anti-endomysial antibodies	12 patients (52.2%) had strict GFD adherence, 11 (47.8%) partial adherence; serological data indicated 19 patients (82.6%) had normal anti-gliadin and anti-endomysial antibodies; 9 (47.4%) reported nonadherence	
Hartman et al (2004)	41 children (mean 11.2 y) and healthy control participants	Bone mineral density in adherent vs nonadherent children	Cross-sectional assessment with healthy control group	Patient and parent self-report and serum anti-endomysial antibodies and anti-tissue transglutaminase autoantibodies	54% of sample classified as nonadherent; nonadherent patients had significantly worse bone mineral density and shorter stature compared with patients adherent to GFD	<p>Data on frequency and patterns of nonadherence not obtained; illustrates effect of nonadherence on health outcome</p>

Study	Sample	Research question	Study design	Adherence measures	Adherence findings	Comments
Kolacek et al (2004)	17 children (mean 5.4 y) and healthy control participants	Chromosome aberrations in lymphocytes before and after GFD	Prospective assessment with healthy control group	Patient self-report questionnaire and serum endomysial antibodies	29% of sample nonadherent to GFD; frequency of chromosome aberrations decreased in adherent patients; unchanged after 2 y in nonadherent patients	Good use of complementary serological data and self-report measures for adherence assessment and illustration of adherence on health outcome in CD; small sample limits generalizability
Kumar et al (1988)	102 adolescents (12–20 y)	Adherence to GFD	Cross-sectional assessment	Patient self-report using classification of consumption	56% of sample had strict adherence, 35% semistrict adherence, 9% complete nonadherence	Self-report assessment used to measure adherence; no information on frequency or patterns of nonadherence
Ljungman and Myrdal (1993)	47 adolescents (12–17 y); 66 control participants	Adherence to GFD	Cross-sectional assessment	Patient self-report questionnaire mailed to patients	81% of patients had strict adherence; 11% moderate nonadherence; 2% significant nonadherence; 6% complete nonadherence; adherence better in girls than boys in patients ages 12–14 than 15–17, and in those at home than in social situations; adherence positively correlated with CD knowledge	High adherence reported likely a function of self-report assessment and inclusion of patients reporting slight nonadherence with patients reporting strict adherence; findings suggest targeting older adolescents and males, and improving education
Mariani et al (1998)	47 adolescents (mean 15.2 y)	Adherence to GFD	Prospective assessment with healthy control group	3-day diet record and serum anti-gliadin and anti-endomysium antibodies	47% of patients with CD at least occasional nonadherence	Patient report adherence assessment supplemented with serological data to identify 5 additional patients who had consumed gluten; good use of multimodal assessment
Mora et al (2001)	19 adolescents (mean 14.2 y); 211 healthy control participants	Effect of long-term GFD on bone density	Cross-sectional assessment	Serum anti-tissue transglutaminase antibodies	53% of sample was nonadherent to GFD; no differences in bone density between adherent and nonadherent patients; bone-specific alkaline phosphatase and N-terminal telopeptide of type I collagen were significantly lower in nonadherent patients	Small sample; supplementary data regarding frequency of nonadherence would be helpful in determining gluten exposure effect on bone density; illustrates potential effect of nonadherence on health outcome
Murphy et al (2002)	44 children and adolescents (mean 3.2 y)	Lactose hydrogen breath test to monitor mucosal healing	Prospective assessment of 21 individuals at 4 and 8 wk follow-up	Dietary interview	9% of sample with persistent lactose malabsorption nonadherent to GFD	No mention of training/reliability of interviewer; authors state nonadherence was corrected with dietary advice, but no details provided; lactose hydrogen breath testing not validated with dietary interview; small sample and low prevalence of nonadherence
Patwari et al (2003)	65 children (mean 8.67 y); 65 healthy control participants	Clinical and nutritional assessment before and after GFD	Prospective assessment with healthy control group	Patient self-report	10.8% of sample nonadherent or with doubtful adherence	Subjective method of adherence assessment used; no details provided for adherence assessment questions, training of interviewers, reliability/validity, or frequency of nonadherence
Rashid et al (2005)	168 children and adolescents (mean 9.1 y)	Clinical features, comorbidities, family history and GFD adherence	Cross-sectional assessment	Patient self-report questionnaire	95% had strict adherence to GFD	Questionnaire not well validated; high adherence rate potentially skewed by social desirability, young age of sample, and variability in reporter; large sample size

Study	Sample	Research question	Study design	Adherence measures	Adherence findings	Comments
Saadah et al (2004)	21 children (mean 7.5 y) with CD and type 1 diabetes	Dietary awareness and adherence to GFD on growth and diabetic control	Prospective assessment with 3-, 6-, 9-, and 12-month follow-up; adherence data cross-sectional	Structured telephone interview with classification	Approximately 80% of patients determined to have acceptable adherence; no significant differences between patients and healthy control individuals on growth parameters	Small sample size precluded sufficiently powered analyses for growth parameters; adherence classification arbitrary and subject to self-report bias; no details provided for scoring criteria; no mention of training/reliability of interviewer; authors cite limitation of serological measures to assess gluten ingestion, and lack of standardized measure of GFD adherence
Selimoglu et al (2006)	36 children and adolescents (mean 10.2 y, 19 with adherence data); 10 healthy control participants	Serum ghrelin levels before and after GFD	Prospective assessment with 6-mo follow-up	Dietary interview by dietitian	10.5% of sample nonadherent to strict GFD; ghrelin levels did not differ significantly as a function of adherence	No mention of training/reliability of interviewer; small sample, subjective assessment of adherence, and lack of data on frequency of nonadherence limit generalization of findings
Seyhan et al (2007)	55 children and adolescents (mean 10.0 y, 28 using GFD)	Prevalence of mucocutaneous manifestations and relation to disease duration and GFD	Cross-sectional assessment	Not documented	35.7% of sample classified as nonadherent to GFD	Method of adherence measurement not documented; small sample
Tommasini et al (2004)	31 children (mean 8 y)	Prevalence of CD using anti-transglutaminase antibody assay	Prospective assessment with 12-, 18-, 22-, and 24-mo follow-up	Parent report interview and anti-transglutaminase antibody assay	Parent reported adherence was 100%, although occasional nonadherence reported in social situations; bioassay nonadherence was 28.5% after 18 mo	Small sample; no mention of training/reliability of interviewer; subjective adherence rates unclear because 100% is reported and occasional nonadherence is stated subsequently in article; no data regarding frequency of nonadherence
Troncone et al (1995)	23 adolescents (mean 14.5 y)	Endomysial antibodies as indicator of nonadherence to GFD	Cross-sectional assessment	7-day dietary recall via structured interview with gram conversion and serum anti-endomysial antibodies	4 (17%) classified as strict GFD adherence; 6 (26%) had 0–0.5 g gluten/day; 6 (26%) had 0.5–2 g gluten/day; 7 (30%) had >2 g gluten/day; only 1 of 6 patients in 0–0.5 g group and only 3 of 6 patients in 0.5–2 g group had endomysial antibodies	Small sample size; no mention of training/reliability of interviewer; dietary intake interview quantified gluten intake according to g/day, allowing good test of utility of endomysial antibodies
Westman et al (1999)	20 children and adolescents with type 1 diabetes mellitus and CD (mean 12.4 y); type 1 diabetes mellitus control group	Growth, diabetes control, dietary intake, and adherence to GFD	Cross-sectional assessment	3-day diet records and food frequency questionnaire; serum anti-gliadin antibodies for patients who had assay within 6 mo of visit	70% of sample nonadherent to strict GFD; of those patients, 30% had trace amounts and 40% had significant amounts of gluten in diet; antiigliadin results available for 60% of sample; no patients had elevations, results not correlated with amount of gluten consumed	Small sample; authors conclude that anti-gliadin antibody data are not helpful in assessing adherence; bioassays drawn on only portion of sample and at different times than dietary intake reporting, thus limiting this conclusion
Yachha et al (2007)	25 children (mean 8.3 y at diagnosis)	GFD on growth and small bowel histology	Prospective assessment with 1-y follow-up	Interview and serum anti-endomysial antibodies	19% nonadherence rate based on bioassay; no interview adherence data reported	Small sample; selection bias for adherence given that criteria included a history of strict adherence to GFD; interview adherence data collected but not reported; no data regarding frequency of nonadherence

6-MMPN = 6-methylmercaptopurine nucleotide; 6-TGN = 6-thioguanine nucleotide; ACTH = adrenocorticotrophic hormone; CD = celiac disease; EF = elemental formula; GFD = gluten-free diet; IBD = inflammatory bowel disease; Ig = immunoglobulin; PF = polymeric formula.