Early diagnosis and management of celiac disease in childhood

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Utilization and effectiveness of E-health technology in the follow-up of celiac disease: A systematic review

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ABSTRACT

Objectives: To systematically review the literature on the utilization and effectiveness of electronic-health technologies (E-health), such as smartphone applications, in managing patients with celiac disease (CD).

Methods: PubMed, Scopus, and the Cochrane Library were all searched (until February 2021). Inclusion criteria were full-text English articles reporting original data on the use of E-health technologies in the follow-up of CD patients, with no age restriction. Exclusion criteria were studies only using non-interactive websites and phone consultation as the primary E-health method. The results were summarized narratively.

Results: Using identified keywords, 926 unique studies were identified. After title and abstract screening by two independent reviewers, 26 studies were reviewed in full text. Finally, eight studies were included in this systematic review, and their quality appraised using standardized forms. Of the eight studies, six were randomized-controlled trials, one mixed-methods study, and one cross-sectional, observational study. Studies were assessed to be of "low" to "moderate" methodological quality. Studied E-health technologies included web-based interventions, smartphone applications, text messaging, and online consultations. The most consistently reported effects were related to improved quality of life (number of studies=4), knowledge on CD (n=3), and dietary adherence (n=2); notably, only one study reported reduced costs of E-health vs. standard (in-office) care.

Conclusions: While E-health has the potential to improve the management of CD, so far, the research in the field is scarce and generally of low-moderate methodological quality. Hence, the effectiveness of E-health in CD management remains uncertain, and more high-quality evidence is required before its utility is known.

INTRODUCTION

Celiac disease (CD) is a chronic immune-mediated disease in which gluten intake causes small-intestinal inflammation and villus atrophy(1). Over the past few decades, there has been a rise in the prevalence of CD, which today affects about 1% of the population worldwide.(2) The disease is associated with various intestinal and extra-intestinal manifestations, including impaired growth and quality of life (QoL),(2) as well as increased costs on individual and societal levels (3, 4). A strict gluten-free diet (GFD) is a cumbersome but effective treatment that can alleviate symptoms and achieve mucosal healing in CD.(5) Patients with CD are recommended long-term follow-up to monitor disease remission and dietary adherence.(6) Electronic-health technologies (E-health) are defined as the use of information and communication technologies, such as software and smartphone applications, supporting health and disease management.(7) Research on E-health technologies has shown positive effects in managing a variety of chronic diseases, including asthma and type 1 diabetes.(8-10) In the care of digestive diseases,(11) including inflammatory bowel disease,(12, 13) E-health technologies have more specifically been reported to improve the patient's QoL and treatment adherence. Besides enhancing the quality of care, E-health holds the potential to reduce costs in healthcare.(14) Although CD is a major public health problem, and despite the potential benefits of E-health technologies in chronic disease management,(15, 16) the evidence of their utility and effectiveness in CD management has not yet been reported. Hence, we aimed to systematically review the literature on the utilization and effectiveness of E-health in the management of patients with CD.

METHODS

Literature search

This systematic literature review was performed following the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines.(17) The literature search was conducted with the support of a professional librarian using PubMed, Scopus, Cochrane Library, and Database of Abstracts of Reviews of Effectiveness. Appropriate search terms were identified from the Swedish version of Medical Subject Headings (MeSH) and the index terms of identified relevant articles. The PubMed search string is presented in Supplementary Table 1, http://links.lww.com/MPG/C720 (the same search strategy was modified to fit the requirements of the other databases).

Eligibility screening

Articles identified until February 2021 were screened against the following, predetermined, eligibility criteria. Articles of any E-health technology used in CD care were deemed eligible. However, telephone consultations (regarded as an established part of standard healthcare) and non-interactive educational websites were not considered E-health, and such articles were hence excluded.(7) Articles limited to non-original data (e.g., reviews), and full-text articles not available in English were also excluded. No further restrictions were applied. Hence, no restriction was made regarding study designs, sample characteristics (e.g., participant's age [children and adults]), outcome measures, and criteria for CD diagnosis.

The article search is depicted in Figure 1 (PRISMA flowchart). Briefly, after duplicates had been removed, articles identified in our database search were screened for eligibility in a twostep process: First, titles and abstracts were screened for eligibility by two independent reviewers (ALM and CMB). The screening was performed in Rayyan, a web application for systematic reviews,(18) where inclusion-exclusion decisions of each reviewer were blinded. Disagreements were resolved in discussion with a third reviewer (KM). Second, full-text articles were retrieved and assessed for eligibility by at least two reviewers (ALM and CMB, in case of disagreements by review of KM). Finally, the reference lists of included studies were screened for additional articles using publication titles (ALM). However, no additional article was identified through this hand searching by title (Figure 1).

Data extraction of included articles

Data from included articles were extracted using a predesigned form and synthesized narratively according to published guidance.(19) The following data were extracted from each article: Study design, sample characteristics (e.g. age, duration of CD diagnosis), number of participants, comparison group, type of E-health technology (e.g. web-based, virtual clinic, etc.), outcome measure, duration of follow-up, and main findings (Table 1). The findings were also reported by the main outcome categorizes (GFD adherence, knowledge about CD and GFD, QoL, patient satisfaction, and other outcomes).

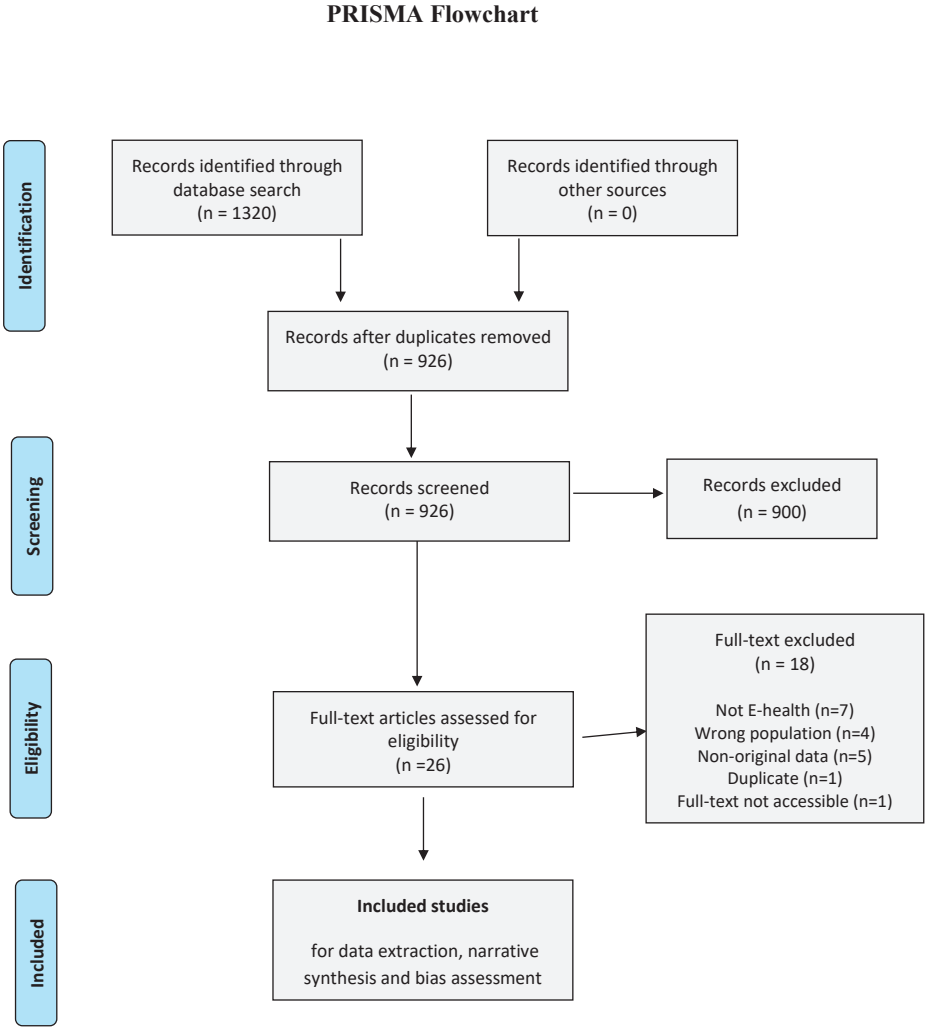

Figure 1. Flowchart of article search and eligibility screening. Literature search within PubMed, Scopus, Cochrane Library and Database of Abstracts of Reviews of Effectiveness (until February 2021). The PubMed search string is presented in Supplementary Table 1. Inclusion criteria were full-text English articles reporting original data on the use of E-health technologies in the follow-up of celiac patients, with no age restriction. Exclusion criteria were studies only using non-interactive educational websites and phone consultation as the primary E-health method.

Bias assessment of included articles

The risk of bias was according to the study design assessed by the revised Cochrane Risk-of-Bias tool for randomized-controlled trials,(20) the Mixed Methods Appraisal Tool,(21) and Joanna Briggs Institute Checklist for Analytical Cross-sectional Studies. (22) The risk of bias assessment was made in agreement with all reviewers (ALM, CMB, KM), and each article was categorized into “low-”, “moderate-” and “high-risk” of bias

Table 1. Included articles on electronic-health technologies (E-health) used in celiac disease (CD) follow-up care.

Authors, Country, (Year of publication)	Design	Participants			Type of E-health	Outcome measures	Follow-up	Main findings
		CD group	Number	Comparison				
Connan *et al.* Canada (2019)(23)	Mixed methods study	Children (mean age 14y) with CD and T1D or their caregivers	18	None	Interactive eLearning module	Satisfaction score, knowledge score.	None	eLearning module efficient for knowledge retention and information access
Dowd *et al.* Canada (2020)(26)	RCT	Adults (>18y) with CD or "gluten intolerance"	115	Wait-list control	Smartphone app, MyHealthyGut	Satisfaction, GFD adherence, QoL, self-regulatory efficacy, anxiety	One month	Improved QoL. Reduced anxiety.
Haas *et al.* USA (2017)(29)	RCT	Adolescents (ages 12-24y) with CD ≥ one year	61	Standard of care	Text Message Educational Automated Compliance Help (TEACH). 45 unique text messages	Primary: CD-specific serology); secondary: GFD adherence (CDAT), patient activation, symptoms, QoL (PROMIS global physical and mental health scales)	Three months	Significantly improved patient activation measurement score, and QoL
Lasa *et al.* Spain (2019)(28)	cross-sectional observational study	Children (ages 4-15y) and adults (23-71y) with CD ≥ one year	Not specified	Other software not containing GFD products	Software for GFD education and nutritional evaluation	GFD energy and nutrient contents	None	GFD evaluation software is a useful tool for GFD nutritional evaluation)
Meyer *et al.* Germany (2003) (24)	RCT	Patients with CD**	64	Standard of care (conventional GFD training)	Computer-based interactive training program	GFD knowledge	Three weeks	Significantly improved GFD knowledge and sustainability

Table 1. Included articles on electronic-health technologies (E-health) used in celiac disease (CD) follow-up care. (*continued*)

Authors, Country, (Year of publication)	**Design**	**Participants**			**Type of E-health**	**Outcome measures**	**Follow-up**	**Main findings**
		CD group	Number	Comparison				
Nikniaz *et al.* Iran (2021)(27)	RCT	Adults (mean age 37y) with CD ≥ six months	60	Standard of care (conventional CD/GFD training)	Persian language smartphone app	CD knowledge, GFD adherence (CDAT)	Three months	Significantly improved GFD adherence. No significant effect on CD knowledge
Sainsbury *et al.* Australia (2013)(25)	RCT	Adults (>16y) with CD	189	Wait-list control	Interactive online intervention	Primary: GFD adherence (CDAT); secondary: GFD knowledge, QoL, psychological symptoms	Three months	Significantly improved GFD adherence and knowledge, that was maintained during follow up.
Vriezinga *et al.* Netherlands (2018)(30)	RCT	Patients ≤25 years with CD ≥ one year	304	Standard of care (in-office consultations)	Online consultation	Primary: CD remission by TTG levels (Point-of-Care test/lab) Secondary: QoL, GFD adherence, patient satisfaction, cost of care	Six months	Improved CD-specific QoL, lower average costs (€93) Sign decreased satisfaction score in intervention group compared to controls (but 48% regarded the online consultation to be as good as outpatient care)

* Primary and secondary outcome measures are detailed if specified in the study.

**Age of participants not reported.

Details on the E-health technologies used in included studies are provided in the Supplementary Results. CDAT, Celiac dietary adherence test; GFD, Gluten-free diet; PROMIS, Patient reported outcome measurement and information system project; RCT, Randomized-controlled trial; TTG, anti-Tissue transglutaminase antibodies

studies. A meta-analysis was not conducted due to heterogeneity between studies. The main reasons for variations between studies were differences in the E-health used (e.g., web-based, virtual clinic, etc.) and outcome measures. Further, there were differences in populations investigated, study designs, and observation periods.

RESULTS

Using identified keywords, 926 unique studies were identified in February 2021. Based on information in the abstracts and titles, 26 studies were reviewed in full text, out of which eight studies(23-30) eventually formed the basis of this systematic review (Figure 1, PRISMA Flowchart). The studies included six RCTs,(24-27, 29, 30) one mixed-methods study,(23) and one cross-sectional observational study (Table 1)(28). Included studies were assessed to be of "low" to "moderate" methodological quality (Supplementary Tables 2 and 3, http://links.lww.com/MPG/C721). Total 811 participants were included in the articles (one study did not report its sample size(28)); four of the eight studies were restricted to adults,(24-27) two included both adults and children,(23) (28) while two studies included only children and adolescents(29, 30). Of the eight included studies, three examined web-based interventions(23-25), three smartphone applications,(26-28) one a telemedicine (text messaging) intervention,(29) and one study examined the use of online consultations (i.e., a virtual clinic)(30). Details on the E-health technologies used in included studies are provided in the Supplementary Results, http://links.lww.com/MPG/C719.

Gluten-free dietary adherence

Five studies(25-27, 29, 30) investigated the effects of E-health interventions on GFD adherence. Of these, two studies, one examining a smartphone application,(27) and one an interactive online training program,(25) reported significantly improved adherence rate in the intervention group compared to baseline measurements and post-intervention controls. Both these studies included adult celiac patient who may had been relatively newly diagnosed (minimum 3-6 months since diagnosis).(27) (25) In contrast, Dowd et al.,(26) examining the effect of a CD self-management application, surprisingly reported that both the intervention group (adult patients with unspecified disease duration) and controls had significantly worsened GFD adherence rate compared to baseline. Neither of the RCTs performed by Haas et al. and Vriezinga et al. found an effect from their interventions on GFD adherence.(29, 30) Both these RCTs were conducted on children or young adults (age <25 years) with a minimum disease duration of one year.

Knowledge about celiac disease and gluten-free diet

Four studies examined the effect of E-health on CD and GFD knowledge.(23-25, 27) All except one study(27) reported significant improvements in CD and/or GFD knowledge of the intervention groups. Connan et al.,(23) including children with a dual diagnosis of CD and type 1 diabetes, saw a small but statistically significant improvement on a CD and GFD knowledge test after an E-learning intervention compared to baseline (p-value=0.001); the Elearning intervention seemed particularly effective in knowledge retention and to provide comprehensive and easily accessible information on GFD. Also, Meyer et al.(24) reported significantly improved knowledge about CD and GFD in adults using a computer-based interactive training program compared to a conventional training program (although both study groups improved their knowledge scores). In the study by Sainsbury et al.,(25) GFD knowledge scores were significantly enhanced in adults using an interactive training program compared to controls. The study by Nikniaz et al. saw no significant effect of their smartphone application on CD and GFD knowledge in adults compared to controls receiving conventional training.(27)

Quality of life

Four studies examined improvements in QoL in CD through E-health technology, one study using a text-message intervention,(29) one a smartphone application,(26) one online consultation,(30) and one study using an online, interactive GFD training program.(25) Two of the studies were restricted to adults,(26) (25) and two on children and adolescents (29) (30). Despite also variations in used E-health technologies as well as QoL instruments used, all studies reported significant positive effects on the QoL of celiac patients; however, in the study of Sainsbury et al.(25) (GFD training program), the improvement was limited to specific aspects of QoL (physical and psychological domains) and not the overall QoL, including for instance also aspects related to social relationships and independence.

Patient satisfaction

Patient satisfaction was measured by questionnaires or semi-structured interviews in three studies using the following E-health technologies: smartphone application,(26), an interactive online training program,(23) and online consultations (30). Most,(23, 26) but not all,(30) studies reported participant satisfaction from using respectively examined E-health technology. Connan et al.(23) reported overall high satisfaction scores with their online GFD education toll used by children (and their caregivers). While Dowd et al.(26) reported that adults with prevalent CD generally found the MyHealthyGut application satisfactory, the participants also said they were unlikely to purchase it or continue using this application after the study. This reluctance was suggested to be related to the application being tailored to more newly diagnosed CD. In contrast, chil-

dren and young adults (aged 2.6-24.1 years) receiving online follow-up care in the study by Vriezinga et al.(30) were significantly less satisfied compared to controls receiving standard (in-office) consultations (p-value=0.001). Compared to controls, participants experienced virtual consultations more impersonal, but found their location and timing more convenient (all p-values<0.02); one third of the intervention group experienced technical problems resulting in lower satisfaction. On the other hand, 48% of the intervention group considered online consultation as equally good as in-office follow-up visits, and 58% wished to continue with online consultations at the end of the study.

Other outcomes

Only one study compared the cost of E-health technology to standard of care. Vriezinga et al.(30) found online follow-up consultations to be, on average, €93 less costly than in-office follow-up (total costs, €143 vs. €236, p-value <0.001). The impacts of E-health on mental health in CD were investigated in two studies.(25, 26) Dowd et al.(26) saw a significant decrease in anxiety measurement one month after the intervention compared to baseline. On the other hand, Sainsbury et al.(25) reported no significant effects from their CD smartphone application on measures of depression and anxiety (all p-values >0.05).

Finally, Haas et al.(29) reported a significant improvement in celiac patient activation (i.e., the ability to self-manage the disease(31)) by the use of a text-message intervention tailored for the disease.

DISCUSSION

This first systematic review on the use of E-health specifically for CD care identified eight studies:(23-30) six RCTs,(24-27, 29, 30) one mixed-methods,(23) and one observational study.(28) Most included studies concluded patient satisfaction with E-health and that its use may be effective in specific aspects of CD care; improved QoL,(25, 26, 29, 30) adherence rate,(25, 27) and knowledge on CD and GFD were among the most consistent findings of this review.(23-25) We found examined E-health interventions to improve the QoL of both pediatric and adult celiac patients.(25, 26, 29, 30) This positive effect on QoL aligns with the results from E-health interventions for other chronic diseases,(11, 13) and may be related to E-health's potential to strengthen the opportunities for patient activation and health education.(32) Speculatively, the better QoL in celiac patients may also be related to an improved GFD adherence rate from studied E-health interventions.(25) Despite inconsistent methodology and outcome measures, two of the included studies reported significantly improved GFD adherence.(25, 27) This finding, though only from

two studies, is encouraging given that strict GFD is a cumbersome treatment, where the prolonged intake of only trace amounts of gluten can cause symptoms,(33) nutritional deficiencies and prevent mucosal healing in CD.(5, 34) Unexpectedly, Dowd et al.(26) found significantly higher non-adherence rates in both intervention and control groups; the reason for this worsened adherence rate is unknown but may be related to the fact that participants at baseline already had an "excellent" to "very good" adherence level. Generally, E-health interventions seem effective in improving nutritional behaviors (e.g., a decreased fat intake and increased intake of fruits and vegetables)(35) and nutritional-related outcomes (e.g., obesity).(36) Disease knowledge is a prerequisite for a patient to manage a chronic disease successfully.(37) The beneficial effects of E-health on CD and GFD knowledge were among the most consistent findings of this systematic review (reported by three out of four studies with that outcome).(23-25) The study by Nikniaz et al.,(27) which did not see an improved CD knowledge, differs from the other studies in using a smartphone application rather than an interactive eLearning/training module. (23-25) However, it is unknown if that difference also explains the difference in results. The use of E-health has for other autoimmune conditions (e.g., type 1 diabetes) been shown to improve illness-related knowledge.(38)

Challenges of implementing E-health into CD care

From our results,(26) and others,(13) it is conceivable that various E-health technologies may better fit the needs of specific groups of CD patients, e.g., defined by disease duration, age and level of disease control. If such associations could be established, it would be possible to tailor virtual CD care to patients' characteristics and specific needs. For instance, while data are limited, we noted that E-health interventions on GFD adherence have so far been more successful in studies of relatively newly diagnosed adult patients rather than studies of children with >1-year disease duration.(27) (25, 29, 30) Barriers to E-health implementation include technology illiteracy and poor internet acceptability. Hence, the adoption and perceived usefulness of E-health for CD could also have geographical differences. A low income and education level have been associated with reduced internet access and use of E-health technology.(39, 40) This has led to concerns that the increased use of digital care might exacerbate socioeconomic gaps in care access. Further, E-health technology has been found to be less accessible to individuals living in rural areas (41) limiting the potential benefits of such interventions on lowering costs and time of travel to care sites. Finally, compared to younger adults, limited internet access and E-health literacy are more common among older people. (40) This age-based disparity is noteworthy given that CD has become increasingly more recognized as a disease in the elderly.(42) However, even younger celiac patients may not necessarily equally appreciate virtual clinics as stand-alone tools for follow-up, compared to in-office care.(30)

Cost reduction is a frequent argument for the implementation of E-health. Indeed, a 2014 umbrella review of E-health in somatic diseases (not including CD) indicated cost-effectiveness,(14) however, this was not a consistent finding and has been contradicted by others.(43) In Colorado, USA, having online access to clinicians was associated with increased use and cost of clinical services compared to those without online access.(44) In the so far only cost-benefit analysis of E-health in CD management, Vriezinga et al.(30) showed a small but significantly decreased cost of a virtual clinic compared to standard outpatient-led care (average cost reduction €93). However, the analysis did not include costs for developing and maintaining the information and communication system required for online consultation, which has constituted a large part of the total cost in other studies.(45) Future cost-benefit analyses of E-health vs. standard follow-up of CD should also include long-term costs, which largely depend on the successful prevention of comorbidities and complications to CD.(3) It is also unknown if E-health may reduce work loss in CD.(4)

Strengths and limitations: Strengths of this study include a thorough literature search in multiple databases using a comprehensive search string. The latter is essential as there are no universal MeSH term indexing E-health studies. A restricted search strategy could hence increase the risk of not identifying all available data. Further, we applied minimal restrictions to our eligibility screening to include all relevant studies in the field, irrespective of patient ages, E-health technology studied, etc. Our use of standardized quality assessment forms and independent reviewers for literature screening and data extraction are additional strengths. This study was mainly limited by the low number of E-health studies on CD care published so far. This scarcity of data, of low-moderate methodological quality, prevented firm conclusions on the effectiveness and utility of E-health in CD care. The lack of data, and their heterogeneity in terms of examined E-health technology and outcome measures, also impeded a meta-analysis of results. The novel coronavirus 2019 pandemic has presented the healthcare system with unprecedented challenges that have necessitated a rapid adaptation to remote care delivery.(46, 47) This transformation of healthcare delivery, including the rise of virtual CD care, should spur more research in this field to support the successful implementation of this technology.

Future research directions

We did not identify any low-risk of bias study for this review (Supplementary Tables 2, http://links.lww.com/MPG/C721 -3, http://links.lww.com/MPG/C722). This highlights a need for higher-quality research on E-health in CD care. Common methodological shortcomings of included studies that should be tackled in future works include high attrition rates and improper or poorly described randomization or blinding procedures.

Opportunities for future research also include a wider use of quantitative disease control measures, such as CD-specific serologies or gluten-immunogenic peptides.(48) Finally, there is a paucity of research analysing the contents and quality of health-promoting applications.(49, 50) Hence, future research should try to assess commonalities ("success factors") in high-effective E-health interventions in CD care.

Conclusions

Although individual E-health studies have shown improvements for specific aspects of CD care, such as QoL and CD knowledge, there are so far insufficient data and a heterogeneity in study methods and targeted outcomes to determine the effectiveness and utility of E-health in CD care. This knowledge gap, combined with increasing demands on healthcare services to provide remote care, should be an incentive for more research.

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