Dietary compliance in adolescents with Celiac Disease

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ABSTRACT

Celiac disease (CD) is a genetically conditioned autoimmune process that appears in about one in 250 people. The disease is caused by a reaction to gluten, a group of various proteins found in wheat and in other grains such as barley and rye. The only effective treatment is a lifelong Gluten Free Diet. Adherence to a Gluten Free Diet is a challenge especially for adolescents for various reasons. Transgressions in diet, however can lead to severe longterm illnesses like osteoporosis and cancer. Within the medical practice it is widely recognised that controlling the follow up of a GFD is important, however there are currently no clear guidelines or procedures to assess the adherence to GFD. In this study three groups of adolescents with CD will take part. Two groups are given apps to assess compliance to GFD, respectively a nongamified and a gamified app, and a control group who is given no app. It is believed that CD patients will improve on GFD compliance without the burden of meeting with a physician or dietist by using the apps. The app highly relies on self-reporting, but also contains a feature for uploading GIP results. Because the app is based on selfreport highly, CD patients can indicate their beliefs about their exposure to gluten in two occasions: in interpretation of their GIP result and in logging their meals. This research involves a mixed method experiment that compares data entry in both apps with standardized structural questionnaires measuring GFD compliance.

CCS CONCEPTS

• **Human-centered computing → Human computer interaction (HCI)**; *User studies.*

KEYWORDS

Celiac, Gluten, Gluten free diet, adolescents, diet compliance, GIP, diet adherence, Mobile Health (mHealth)

1 INTRODUCTION

Celiac disease (CD) is a genetically conditioned autoimmune process that appears in about one in 250 people. The disease is caused by a reaction to gluten, a group of various proteins found in wheat and in other grains such as barley and rye [19]. Celiac disease can develop at any age, and slightly predominates in females [9]. Symptoms range from the classic signs of malabsorption syndrome — diarrhea, weight loss, growth failure, osteoporosis, and anemia — to nonspecific symptoms such as chronic constipation or abdominal pain [15]. Research has also indicated that a majority of people are asymptomatic, while having the disease. Therefore most people remain undiagnosed if they are not actively screened [21].

The only effective treatment is a strict and permanent gluten-free diet (GFD). The effectiveness of such a diet produces significant clinical improvement in not only digestive symptoms, but also in the extra intestinal symptoms associated with CD [4, 22]. However, the level of compliance to such a diet is difficult and poor, especially in adolescents between ages of 12 and 17[28, 30]. Compliance with GFD in adolescents has been reported to be between 52% and 81% [28]. Poor compliance is attributed to stigmatisation and isolated feelings in social situations, as well as lack of knowledge regarding CD an GFD [30]. Within the family environment adolescents seem to struggle with adherence to GFD al lot less than when socializing with friends. These situations may lead to transgressions, which are often associated with feelings of anger and envy. Thus, adhering to GFD has an impact on not only food consumption but also on the general lifestyle and quality of life (QOL) of individuals with CD. Wagner(2008) found that adolescents who were noncompliant with their GFD experienced a lower general QOL, especially lower physical health, with a higher feeling of ill-being, more family problems, and problems in their leisure time. CD-associated burden has been highest in patients with frequent dietary transgressions. They anticipated their future would be more difficult. [28].

Adolescents who were diagnosed with CD in their childhood seem to experience more dilemmas adhering to a GFD related to eating out, peer pressure and cross-contamination as they grow older. Cross contamination appears when people who ate or touched gluten products inadvertently drop fragments of gluten[20, 26]. Furthermore, patients diagnosed later in life, seem to have more difficulty adhering to a GFD than patients who have been diagnosed in early childhood [28].

Transgressions in diet delay patient recovery. If transgressions are frequent, various types of associated long term complications may appear [27]. Factors that improve chances of compliance are: early diagnose, presence of symptoms after ingestion, a good awareness in family and patient, frequent follow-ups by nutritionists or physicians. A study by Ciccocioppo (2015) states that *"patient 's education, close supervision with scheduled nutritional counselling and maintenance of dietary adherence when travelling or dining out, are all crucial factors needed to achieve full compliance"* [5]. Persistence of symptoms are generally related to irregular, or poor dietary compliance, or - clearly - with continued gluten consumption, specially in adolescents[20].

2 DIETARY COMPLIANCE MEASUREMENT

Although the importance of controlling the follow up of the GFD is widely recognised, there are no clinical guidelines that guarantee results, nor are there procedures to assess the adherence to a GFD and the transgressions that occasionally occur. At the moment most clinical monitoring of diet compliance is done by

- clinical follow up visits
- visits to expert nutritionists (self reports)
- serological time controls of antibodies
- serial endoscopies
- structural questionnaires and
- determination of gluten peptides from gluten in faeces or urine.

All of these procedures have proven to be useful when applied, alone or in combination, depending on the cases. These methods are quite expensive and time consuming as they require specialist

time and effort to consult the patient and analyse the results. Furthermore, Serological time controls of antibodies are not effective when changes in antibodies are small and endoscopies are quite unpleasant, next to it's effectiveness being maximised only for cases that are not associated with clinical improvement or serological changes [20].

2.1 Follow ups and Self reports

Monitoring of compliance is often done by repeated administration of questionnaires, but these are not always available in all centers[20]. Furthermore follow ups are often not visited. Patients indicate that they are managing their CD on their own, especially when symptoms reduce or disappear. When quality of life and disease specific symptoms worsen however, patients are more likely to visit a follow up. Remarkable however is, that when patients make dietary transgressions, they are less likely to visit a follow up [13].

Silvester (2017) noted an important finding concerning selfreports in GFD compliance: reports that do not facilitate for the possibility of unintentional gluten ingestion overestimate GFD adherence. Individuals who believe they are following a GFD are not readily able to correctly identify foods that are GF, which suggests ongoing gluten consumption may be occurring, even among patients who believe they are “strictly" adherent [25].

2.2 Structural Questionnaries

Structured short questionnaires are used as an alternative to consultations with a dietician to obtain a rapid assessment of the adherence to the GFD. It is easy to complete this type of questionnaire in the patient’s usual clinic. The responses are highly correlated with antibody levels and the presence of VA in duodenal biopsies and useful for monitoring. In general, questionnaires are easy to administer and often complement each other. They not only assess the quality of life, in a general or specific way, but also are able to estimate the changes occurring after the follow-up of the GFD[20].

2.3 Biomarkers

Biomarkers, also called gluten immunogenic peptides (GIP) are far less invasive and promising when it comes to accurately detecting gluten in food [20]. They look like a pregnancy predictor stick and are used in the same manner. A big advantage compared to other methods of selfreporting, questionnaires of follow ups is that this method generates an accurate measure of dietary adherence in an non invasive way and can be linked to gluten exposure directly. Therefore GIP, being easy to use and relatively inexpensive, enables a direct and quantitative assessment of gluten exposure [23].

3 GOALS

Former research has made three things clear:

a) There is no clinical guideline or procedure to assess adherence to GFD, even though the necessity of monitoring CD patients is widely recommended.
b) Adolescents have difficulty adhering to a GFD for various reasons.
c) Some currently used methods for dietary compliance measurement are not always reliable, on top of being expensive, patient unfriendly and time consuming.

This study aims to improve GFD compliance by using a custom made health monitoring mobile app as a new method for monitoring GFD compliance in adolescents with CD. It does so by trying to improve frequency of selfreporting in relation to food intake, experiencing symptoms, perceived energy levels and using a biomarker that indicates gluten intake in urine. In doing so, it is believed that patients will improve on GFD compliance without the burden of meeting with a physician or dietist. The app highly relies on self-reporting, but also contains a feature for uploading GIP results. Because the app is based on selfreport highly, patients can indicate their beliefs about their exposure to gluten in two occasions: in interpretation of their GIP result and in logging their meals. This way Sivester 's (2016) notion about unintentional gluten intake has been taken into account within the design of the app.

There will be two versions of the same app: a regular version that has implemented theories around behavioural change and a gamified version, which adds gamification concepts to it. Both versions will be compared to each other in terms of GFD compliance and improvement of GFD compliance and rate of logging events.

3.1 Definitions

Diet adherence The WHO defines adherence as *"the extent to which a person's behaviour – taking medication, following a diet, and/or executing lifestyle changes, corresponds with agreed recommendations from a health care provider"* [17]. Studies over the years have conflicted with what they consider to be "safe" thresholds for gluten intake on a gluten-free diet. Some have suggested that 625 milligrams (mg) per day (roughly one-fifth a slice of bread) is perfectly fine, while others raise the red flag at anything over 10 mg per day (1350th of a slice). In general, if your gluten intake is less than 10 mg a day most people are fine. A typical western european diet contains about 20 grams of gluten per day[6].

mHealth Mobile Health (mHealth) aims at delivering healthcare services regardless of any mobility constraints, i.e. overcoming geographical, temporal, and organizational barriers. It supports direct access to health services regardless of time and place and allows to reduce high costs of existing national health services. Indeed, it empowers patients and families to self-care being suitable to help address chronic and lifestyle related diseases [1].

Health related Quality of Life (HRQoL) HRQoL focuses on the aspects of QoL that are affected by health. For example, HRQoL is defined as *”those aspects of self-perceived well-being that are related to or affected by the presence of disease or treatment”*. Many HRQoL measures are in fact measures of self-perceived health status [14, 32].

4 MONITORING HEALTH USING M-HEALTH TECHNOLOGIES

mHealth technologies have recently been implemented as patient self-management tools in the treatment of chronic diseases such as diabetes mellitus, lung disease, cardiovascular disease and kidney disease [31]. Researchers believe the ease of access to resources that mHealth technology provides can augment the patient's ability to engage in self-care activities, and may lead to better patient health outcomes, well-being, and QoL [29].

Hamine et al. (2015) conducted a systematic review looking at adherence rates and patient outcomes after using mobile device mHealth interventions (e.g., SMS, video messaging, electronic medication monitoring) in 107 studies on diabetes mellitus (67/107), chronic lung diseases (19/107), and cardiovascular diseases (27/107). Out the 107 studies reviewed, 50 of these were randomised controlled trials (RCT) with 56% showing significant effects on adherence. The other 67 studies were qualitative, providing user feedback and critical data on how and why mHealth tools impacted adherence behaviours [11].

Whitehead et al. (2016) reviewed the effectiveness of self-management mobile phone and tablet apps in long-term condition management in nine studies on diabetes mellitus (5/9), chronic lung disease (3/9), and cardiovascular disease (1/9) from 2005 to 2016. Six of the nine studies demonstrated statistically significant improvement in symptom control [31].

mHealth interventions used in CD patient management/monitoring are scarce. Some have used SMS text reminders, online educational courses, and evidence-based nutritional advice in the form of a smartphone application [7, 10, 24]. Other apps have been focusing around the social aspects surrounding CD in providing for support about food, restaurants and a patient sharing platform [2]. One app that is trying to monitor foodintake and symptoms along with other functionalities about Celiac Disease is MyHealthygut. This app has been used in a study addressing GFD adherence and came with interesting results. After using the MyHealthyGut app, participants reported improvements in psychological outcomes, but dietary adherence over the time course of a month worsened in both experimental groups. However symptoms in the second experimental group reduced significantly after having used the app, which might be a strong indicator of the effectiveness of using apps for GFD monitoring [8].

5 METHOD

This study is part of an ongoing Erasmus+ research project which has been running over the last 3 years. Therefore the methodology used is in many ways similar to previous research within the same project with different apps and games, enabling comparison between the studies in the future. App functionalities have been improved and iterated upon given previous user feedback. During this study mobile phones are used as input device for the first time and the usage of a gamified version is entirely new.

This study, as in all previous studies, aims to improve GFD compliance by using a custom made health monitoring app as a new method for monitoring GFD compliance in adolescents with CD. The app highly relies on self-reporting, but also contains a feature for uploading GIP results. The experiment will contain Structural Questionnaires, Self report and biomarker methods, in which the structured questionnaires will be used for validation of the data gathered through the app, but they will not be part of the app itself.

5.1 Two apps, AB testing

Subjects of this experiment will be divided into three groups. One group (A) will not be given an app (control group) One group (B) will be given a non-gamified version for GFD monitoring with a notification system concerning motivational aspects. Last group (C) will be given a gamified version of GFD monitoring with a notification system concerning gamified motivational aspects.

The experiment will run during a timespan of 21 days, also called *"The 21 day challenge"*.

The non-gamified version consists of 4 main hubs that facilitates data entry about food intake, symptoms, perceived energy level and GIP results. Within the screens of food intake and GIP results subjects can indicate whether or not they think gluten were involved. This way unintentional gluten ingestion or misinterpretation of GIP results can be noticed. The other features involve an overview page of loggings per day and an overview page of loggings per week and a goal setting feature for data entry on the fore mentioned aspects. The amount of loggings is continuously given as feedback to the user in the mainscreen of the app and in weekly reports (mail intervention).

The gamified version has the same functionalities concerning data input by the subjects, but has two gamified aspects.

- medals, in which subjects achieve levels after completing certain tasks or streaks. Medals are used to obtain XP.
- avatar customization, in which subjects are allowed to change the clothes of the avatar based on XP they have gathered.

In all groups a selective amount of X subjects will be given a box of GIP sticks to take home. The amount is limited because at current time of the experiment, not enough GIP sticks are available to provide for all participants. The exact amount of GIP sticks that will be provided for is at time of writing unclear. Subjects not receiving GIP will be given a version of the app without the GIP logging feature.

5.2 Participants

This experiment is executed within a medical context. Therefore ethical approval will be obtained from the Ethics board at Institute of Technology, Carlow. Recruitment will be facilitated by the Celiac Society of Ireland who provides assistance contacting willing participants. Participants should be between 12 and 25 years old and in possession of a confirmed medical diagnosis of celiac disease with a positive blood test or biopsy by the participants' physician. Prior to the study each participant signs an informed consent form.

5.3 Procedure 21 day challenge

Subjects will be provided with an information sheet concerning the experiment and they will be asked to sign a consent form.

Subjects will be asked to fill in two validated structural questionnaires online before and at the end of the experiment, that will take 5 minutes alltogether.

CDAT (Celiac Dietary Adherence Test) CDAT consists of seven structured questions about compliance and is scored on a Likert scale from 1 to 5, so that summing the values obtained gives an overall score from 7 to 35. Values less than 13 are considered to show good compliance, while those over 17, represent intermediate or low adherence [16].

PAM (Patient Activation Measure) The Patient Activation Measure is a valid, highly reliable, unidimensional, probabilistic Guttman-like scale that reflects a developmental model of activation. It consists of 13-items and scores range from 0 to 100; higher scores indicate greater patient activation. Activation appears to

involve four stages: (1) believing the patient role is important, (2) having the confidence and knowledge necessary to take action, (3) actually taking action to maintain and improve one's health, and (4) staying the course even under stress. The measure has good psychometric properties indicating that it can be used at the individual patient level to tailor intervention and assess changes[12].

After having filled in the standardised questionnaires subjects are asked to download and install the app on their phones. From that moment on, the 21 day challenge has started and data entry may begin. During the challenge the app groups will both receive notifications at set times and at the end of each week they will receive a weekly report by mail, which can also be found in the app itself.

At the end of 21 days, subjects will again be asked to fill in CDAT and PAM questionnaires, in addition to an app usability questionnaire. The latter, ofcourse will not be given to the control group. The usability questionnaire consists of fifteen questions that are divided into two sections and is used in a previous version of the 21 day challenge with web-based apps. The first section (questions 1-7) is designed to identify each healthcare practitioner's experience with technology and electronic devices, whereas the second section of the questionnaire (questions 8-15) looks to identify their attitudes beliefs of mHealth technology. The questions included in the questionnaire are influenced by similar themes used by [3, 18, 29] who looked at perceived positive effects and barriers of mHealth technologies, previous experience with technology, attitudes and beliefs towards mHealth technologies, and current knowledge of mHealth technologies/telemedicine, respectively.

5.4 Variables

Control group and app groups will be compared on the following aspects with the goal to find out which of those has better GFD adherence and which of those yield higher Patient Activation Measures. Hypothesis is that the app version groups (B and C) yield significantly higher scores on both validated tests (CDAT and PAM) compared to the control group (A).

Both app versions will be compared on the following aspects:

- logging intervals and frequency on all 4 input features (statistically analysed per feature)(3 features for the groups without GIP): data, food, energy and GIP.
- perceived diet adherence based on data submitted in food feature of the app
- actual GFD compliance based on data about symptoms and GIP feature, compared with data from CDAT for correlation
- perceived energy based on energy level feature in the app, compared with PAM data for correlation
- app usability based on questionnaire
- influence of notifications based on logging intervals and frequency after notifications have been send.
- transgression frequency by looking at the GIP, symptom and food diary data. Both correlation within app, as well as comparison between apps.

Hypothesis is that the gamified app (C) will perform significantly better on all aspects mentioned above than the non-gamified app.

5.5 Statistics

The following statistical methods will be used:

(1) Bayesian AB testing to test control group against app group for CFD compliance and PAM scores. A vs. B and C.
(2) Bayesian AB testing on the above mentioned hypotheses involving comparison between above mentioned variables of versions B and C.
(3) Pearson's correlation within app between entered data about GIP results, symptoms, food intake and energy levels
(4) Pearson's correlation between entered questionnaires and entered app data within each testing group.

Correlation data tell us something about the usefulness of the app for measuring CFD compliance, whereas the Bayesian AB testing tells us something about the usability of certain implemented features.

6 PLANNING

schedule	
22-26 March	finalize non gamified design. Finalize design doc on gamified app
29 - 2 April	Design gamified app. Bug testing non gamified app. Finalize notification system (implement TEACH research findings in system)
5 - 9 April	Design gamified app, finalize medal system
12 - 16 April	Design gamified app, finalize avatar system
19 - 23 April	Test gamified design (Figma prototype for usability issues) and test gamified app for bugs(development)
26-30 April	Springbreak
3 - 7 May	Prepare Experiment "21 day challenge". Kick off experiment. Write paper up to results section.
10-14 May	2nd week 21 day challenge. Feedback supervisor on paper.
17 - 21 May	3rd week 21 day challenge. Final data collection post experiment Questionnaires.
24 - 28 May	Gather data. Statistical analysis of the data. Write results section.
31 - 4 June	Gather data. Statistical analysis of the data. Write results section.
7- 11 June	Write Discussion. Feedback on results section from supervisor.
14-18 June	Finalize paper. Feedback Discussion section from supervisor. Hand in paper.
21 - 25 June	Prepare defense presentation
27 - 2 July	Defense presentation

7 RISK ASSESSMENT AND BACKUP PLANS

At the moment there are three main risks concerning the execution of the experiment.

(1) **The apps are unfit for testing with CD patients. They are not bug free.**
The likelihood that none of the apps will be working properly is very small. At the moment development team is working hard on getting the non-gamified app to work. In case the gamified app is not ready for testing, we could only test the non-gamified one and compare with the no app control group. Furthermore, both designs will be ready for testing as a clickable prototype (but no data will be gathered on GFD compliance). This way usability can still be measured but the usefullness will be impossible to test.

(2) **Covid19** The experiment relies to great extend on medical staff in providing the subjects with GIP sticks.
The production and availability of GIP sticks however is more of a concern. Due to Covid19 medical production has been lower than usual and GIP sticks, being a relatively new way of testing for gluten are not readily available. In this case the GIP feature are left out of consideration in this study.

(3) **Trouble with finding CD subjects**As last year all medical research had been postponed due to Covid19, the experiment could not take place as planned. Then the experiment was done with scholars without CD disease, which yielded data about app usage, but not about CFD compliance. This year however things are looking better. There has been made contact with the Celiac Society of Ireland and they have said to be willing to collaborate. This society has 7000 celiac patients subscribed in their database. All will be asked to collaborate in this experiment. If somehow, still CD patients may not be willing to participate in this experiment, we could try and find CD patients in the Netherlands that want to participate on a voluntary basis. This would mean a delay in the execution of the experiment.

(4) **Too little data** The apps rely to great extend on willingness and frequency of selfreports. Data entry by CD participants is pivotal. If no one will enter data, or will enter too little data during the 21 day challenge, there is nothing or too little to be analysed. In this case we'll have to seriously evaluate the apps and the systems behind it and compare design decisions made to already existing mHealth apps used for monitoring diet or medicine intake. This study will then become more of a literature study in stead of an user study.

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