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Survey on computer aided decision support for diagnosis of celiac disease

Sebastian Hegenbart [a,*], Andreas Uhl [a], Andreas Vécsei [b]

[a] Department of Computer Sciences, University of Salzburg, Jakob-Haringer Strasse, 5020 Salzburg, Austria
[b] St. Anna Children's Hospital, Medical University Vienna, 1090 Vienna, Austria

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ABSTRACT

Celiac disease (CD) is a complex autoimmune disorder in genetically predisposed individuals of all age groups triggered by the ingestion of food containing gluten. A reliable diagnosis is of high interest in view of embarking on a strict gluten-free diet, which is the CD treatment modality of first choice. The gold standard for diagnosis of CD is currently based on a histological confirmation of serology, using biopsies performed during upper endoscopy. Computer aided decision support is an emerging option in medicine and endoscopy in particular. Such systems could potentially save costs and manpower while simultaneously increasing the safety of the procedure. Research focused on computer-assisted systems in the context of automated diagnosis of CD has started in 2008. Since then, over 40 publications on the topic have appeared. In this context, data from classical flexible endoscopy as well as wireless capsule endoscopy (WCE) and confocal laser endomicrosopy (CLE) has been used. In this survey paper, we try to give a comprehensive overview of the research focused on computer-assisted diagnosis of CD.

1. Introduction

Celiac disease (CD) is a multisystemic immune-mediated disease, which is associated with considerable morbidity and mortality [4,44,82]. The prevalence of CD in Europe and North America ranges from 1:80 to 1:300 [11,12,28,29,32,61,66]. In the pathogenesis of CD, a pivotal contribution is made by a dysregulated immune response directed against tissue transglutaminase type 2 (TG2) which has been identified as a prominent autoantigen of CD [27]. The exogenous trigger of this dysregulated immune response is gluten which is ingested along with grain-containing food. Gluten is the main protein of specific grains like wheat, barley and rye.

CD displays itself through a wide spectrum of clinical manifestations including gastrointestinal symptoms such as abdominal pain, chronic diarrhea, bloating, nausea and vomiting as well as more general features like failure to thrive, weight loss and fatigue. There are also numerous extraintestinal CD manifestations like dermatitis herpetiformis [6,97], alopecia areata and cerebellar ataxia [47] and various other neurologic and psychiatric diseases, iron deficiency [65] and premature osteopenia. It has been estimated that seven out of eight patients with CD remain undiagnosed because most cases of CD only have minor gastrointestinal symptoms [13].

In untreated or inappropriately treated CD the inflammation caused by the dysregulated immune response can disrupt the intestinal mucosa thus leading to a total atrophy of the villi, which are finger-like projections of the mucosa. After embarking on a strict gluten-free diet (GFD), which is the CD treatment modality of first choice, the inflammation gradually subsides allowing for mucosal healing. Strict adherence to a GFD for life is required if acute and chronic complications are to be avoided [88]. To avoid the most severe complications of CD, early and reliable diagnosis of CD for commencing a strict GFD is of vital importance.

Besides for a small proportion of children fulfilling certain clinical, serological and genetic criteria [64], biopsy of the small intestine remains the gold standard for CD diagnosis and is usually recommended as CD requires a lifelong commitment to a strict GFD.

The mucosal alterations caused by CD are classified into different stages of severity. Oberhuber [77] modified a widely used staging of severity by Marsh [75] in 1999. This histological classification scheme identifies six classes, ranging from class Marsh-0 (no visible change of villi structure) up to class Marsh-3C (absent villi).

Unfortunately, the histological staging of biopsies is subject to a significant degree of intra- and inter-observer variability [76,1,85,96,23]. Therefore, observer independent diagnostic methods such as computer-assisted diagnosis systems are urgently needed. Furthermore, the whole diagnostic work-up of CD, including duodenoscopy

* Corresponding author. Tel.: +43 662 8044 6305; fax: +43 662 8044 172.
E-mail addresses: shegen@cosy.sbg.ac.at (S. Hegenbart), uhl@cosy.sbg.ac.at (A. Uhl), andreas.vecsei@stanna.at (A. Vécsei).

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with biopsies, is time-consuming, cost-intensive, and rather invasive. Consequently, to save costs, time, and manpower and at the same time increase the safety of the procedure, a less invasive approach avoiding biopsies would be highly desirable. Recent studies by Cammarota et al. [10,8] investigating such endoscopic techniques report reliable results. Current diagnostic methods are entirely observer-dependent and require significant knowledge, expertise, and time.

An interesting field where computer-assisted video analysis could be useful is the application within follow-up endoscopies of celiac patients on a GFD, testing if a re-growth of villi has taken place. Another advantage of computer-assisted video analysis is quality improvement rendered possible by means of telemedicine, for example, by obtaining a second opinion after endoscopic video clips have been transmitted to institutions that have video analysis software at their disposal allowing for an observer independent objective diagnostic evaluation.

A further limitation of the current gold standard for the diagnosis of CD is due to the possibly patchy distribution of intestinal mucosa areas affected by CD in the midst of normal mucosa [5,62]. If, unfortunately, biopsies are taken only from areas of healthy mucosa within the duodenum the proper diagnosis of CD will be missed due to sampling error. A diagnostic tool based on computer-aided pattern analysis of endoscopic video clips could indicate areas that are damaged by CD thus improving the targeting accuracy of biopsy. Additionally, such a system would allow gastroenterologists who do not routinely take duodenal biopsies recognize mucosal alterations triggering a decision to biopsy. So even in a diagnostic scenario involving biopsies, computer-assisted video analysis contributes to a more reliable diagnosis.

In this work, we try to draw a comprehensive picture of the research focused on computer-assisted diagnosis of CD in endoscopic data. In Section 2 an overview of current endoscopic techniques used in automated diagnosis is given with a discussion of the different properties and requirements for computer-assisted systems. Section 3 provides a general overview of techniques devised for classification of CD. Concepts for handling image degradations in the challenging endoscopic environment are presented in Section 4. Common issues and flaws in the methodical evaluation of techniques and the available ground-truth in medical image classification are covered in Section 5. Finally, Section 6 concludes the paper.

2. Endoscopic techniques used in diagnosis of celiac disease

Besides standard upper endoscopy, several new endoscopic approaches for diagnosing CD have been applied [14] and used in research on computer-assisted diagnosis. The modified immersion technique (MIT [7–9]) allows detailed scanning of the mucosal surface for villi. Technically, water is rapidly instilled into the duodenal lumen after evacuation of air by suction through the endoscope. Villi, if present, straighten up in water and appear as tiny finger-like structures. In a detailed evaluation, Hegenbart et al. [52] have presented strong empirical evidence, that MIT is superior for computer-aided diagnosis as compared to the conventional imaging technique.

Narrow band imaging (NBI [30]) uses specific blue (440–460 nm) and green (540–560 nm) wavelengths for illumination to enhance the contrast of vascular patterns on the mucosal surface. This imaging modality could be a promising technique for classification of celiac tissue. Valitutti et al. [90] recently proposed the use of NBI combined with the water immersion technique which could also be explored for automated diagnosis. At this point in time, a systematic assessment of all four imaging modalities in flexible endoscopy for computer-assisted diagnosis is still open.

Confocal laser endomicroscopy (CLE, also known as visual biopsy) is a novel technology allowing real-time in vivo microscopy. CLE allows the inspection of multiple mucosal layers, employing a laser at different focal points and has been shown to be a promising technique for diagnosis of CD in endoscopy [70].

A general drawback of endoscopy using flexible endoscopes is the limited range. As a way of inspecting a much larger area of the intestine, wireless capsule endoscopy (WCE [80]) is used. In WCE, a small capsule equipped with a camera is swallowed by the patient. The capsule records images of the mucosal tissue during its passage through the intestine, which is then analyzed by a clinician or potentially by an automated system for diagnosis.

Figs. 1 and 2 schematically illustrate the different endoscopic techniques used for computer-assisted diagnosis of CD.

2.1. Endoscopic markers and diagnosis of CD

The most prevalent endoscopic markers for CD include scalloped folds, mosaic patterns of the mucosa and a nodular mucosa [25]. After entering the duodenum with the endoscope, the endoscopist searches for visible CD-induced mucosal lesions indicated by these markers. All of this features become more pronounced and easier detectable when using MIT. Consequently, NBI is employed (if available) to specifically delineate the outline of the residual villous structures (if present). NBI is used because images captured using this modality allow a better assessment of the villous height and shape compared to the conventional white light endoscopy.

It has been reported that the prevalence of endoscopic markers is significantly lower for partial villous atrophy (58%) than for subtotal or total villous atrophy (82%) [26]. Consequently, systems

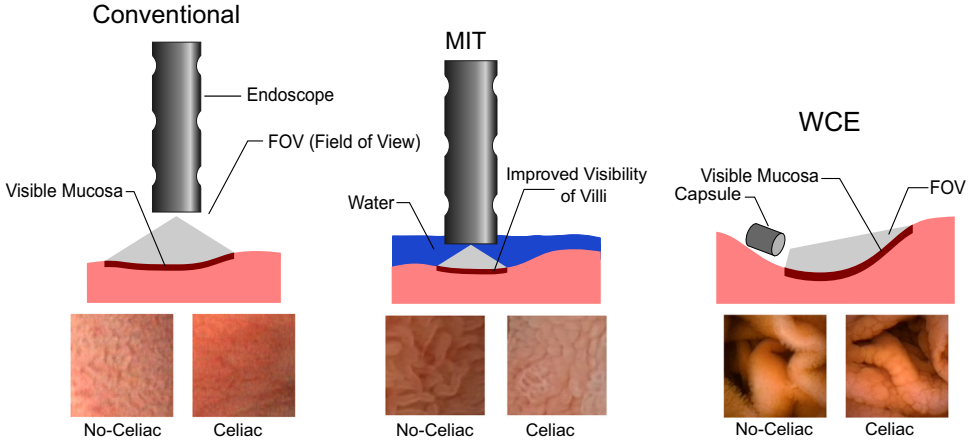

Fig. 1. Conventional endoscopic imaging, the modified immersion technique (MIT) as well as wireless capsule endoscopy (WCE).