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Suggestions for automatic quantitation of endoscopic image analysis to improve detection of small intestinal pathology in celiac disease patients

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ABSTRACT

Although many groups have attempted to develop an automated computerized method to detect pathology of the small intestinal mucosa caused by celiac disease, the efforts have thus far failed. This is due in part to the occult presence of the disease. When pathological evidence of celiac disease exists in the small bowel it is visually often patchy and subtle. Due to presence of extraneous substances such as air bubbles and opaque fluids, the use of computerized automation methods have only been partially successful in detecting the hallmarks of the disease in the small intestine—villous atrophy, fissuring, and a mottled appearance. By using a variety of computerized techniques and assigning a weight or vote to each technique, it is possible to improve the detection of abnormal regions which are indicative of celiac disease, and of treatment progress in diagnosed patients. Herein a paradigm is suggested for improving the efficacy of automated methods for measuring celiac disease manifestation in the small intestinal mucosa. The suggestions are applicable to both standard and videocapsule endoscopic imaging, since both methods could potentially benefit from computerized quantitation to improve celiac disease diagnosis.

1. Clinical and quantitative background

The diagnosis and treatment of celiac disease is a ubiquitous problem throughout the world. In part this arises from the fact that the disease varies widely in its presentation [1,2]. The protein gluten, found in wheat, rye, and barley grains, is toxic to celiac disease patients and causes damage to the small intestinal mucosa [2]. Since abnormality may not be evident in small intestinal endoscopic images, however, the diagnosis of the disease can be difficult. For definitive diagnosis, there should be histologic confirmation of the intestinal damage in serologically positive individuals [3]. Improvement on a gluten-free diet is added evidence that the patient has this disorder [4]. Furthermore, celiac disease is associated with the HLA genotypes DQ2 or DQ8 [5]; however, testing for these alleles has limited sensitivity and specificity [6]. When a celiac patient has been diagnosed, treatment with a gluten-free diet is typically the first and only therapy [7].

Another difficulty in the diagnosis of celiac disease is that currently-used pathological scoring techniques are only semi-quantitative. The modified Marsh criteria were developed to gauge the degree of abnormality found when observing pathology slides of small intestinal villi under light microscopy [8]. Marsh type 0 patients are normal. Marsh type I patients have an increase in intraepithelial lymphocytes in the jejunum and duodenum. In Marsh type II, there is hyperplasia of intestinal crypts but normal villi. For Marsh type III, there is increased crypt hyperplasia and presence of villous atrophy ranging from mild (type IIIa), to marked (type IIIb), to complete (type IIIc). Clinical scoring is therefore to some extent qualitative and subjective, with limited efficacy. Since the presence and even the degree of villous atrophy is spatially patchy [9], different biopsies from the same patient may be assigned different Marsh scores.

When celiac disease is undiagnosed and untreated, it can result in maladies. Insufficient absorption of nutrients, minerals, and fat-soluble vitamins is common in these patients [10,11]. There is also an increased risk of malignancy including adenocarcinoma, lymphoma of the small bowel, and other non-Hodgkin's lymphomas [12]. Ulcers may form, particularly at the level of the jejunum, and there can be narrowing of the small bowel with the possibility of complete obstruction as a result of scarring [13]. Calcium and vitamin D malabsorption can occur and result in osteopenia or osteoporosis. There may also be bacterial overgrowth of the small

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intestine due to the lack of normal absorption, which can cause or worsen the malabsorption [14].

1.1. Evaluation of clinical status with videocapsule endoscopic imaging

The use of videocapsule endoscopy rather than standard endoscopy for detection of pathology is advantageous for its limited invasiveness and coverage of the entire small intestine, although biopsies cannot yet be obtained with this method. However, in studies in which videocapsule endoscopy was compared with conventional upper gastrointestinal endoscopy with duodenal biopsy as a gold standard, the videocapsule method has been shown to have good sensitivity (85.0–87.5%) and specificity (100–90.9%) for the diagnosis of celiac disease [15,16]. Videocapsule endoscopy was also shown useful to detect small intestinal villous atrophy in patients with biopsy-proven celiac disease with 92% sensitivity and 100% specificity [17]. Detection of other mucosal abnormalities, exclusion of adenocarcinoma, and identification of signs of ulcerative jejunoileitis or intestinal T-cell lymphoma has also recently been done using the videocapsule method [18,19]. Thus videocapsule endoscopy has a similar capability as compared with standard endoscopy to characterize patient clinical status, and can be useful for automated analysis.

There can be marked differences in standard or videocapsule images obtained from celiac patients with pathology as compared with normal patients, and the goal of any quantitative automated system is to detect both marked and subtle pathology. In Fig. 1, examples of videocapsule images are shown at the level of the duodenum. Panels A and B are from control patients without celiac disease or villous atrophy. Panels C and D are from celiac patients prior to following a gluten free diet. The control patients have mucosal folds with smooth edges (panels A and B). The mucosal surface itself is approximately consistent in texture and appearance in all image areas in panel A, and also for all image areas in panel B. There are evident fine surface projections at the limit of resolution which represent either villi or clusters of villi. In panel C, the surface is greatly mottled. In panel D, the edges of the mucosal folds are highly scalloped. The appearance of the small intestinal mucosa in panel C and D are typical of areas with substantial pathology in untreated celiac patients. Although measures have yet to be devised to numerically gauge the severity of abnormality throughout the small intestine, the extent of villous atrophy can be approximated by measuring the time in which abnormality is observed as a percentage of total small bowel transit time [20]. This can be done by simply counting the number of images with evident pathology, versus the total number of images in the series taken at the level of the small intestine.

1.2. Automated quantitative systems

Based on the difficulty in diagnosis and characterization of celiac disease, the large proportion of undiagnosed patients with the disease [21], and the potential for severe complications when untreated, there is a significant need for improved quantitative and automated diagnostic methods. Most helpful would be the possibility to provide an actual Marsh score based upon a computerized endoscopic imaging and quantitative analysis paradigm. The ultimate goal of such a system should be to provide a continuous score, that is, a score using numbers with decimal

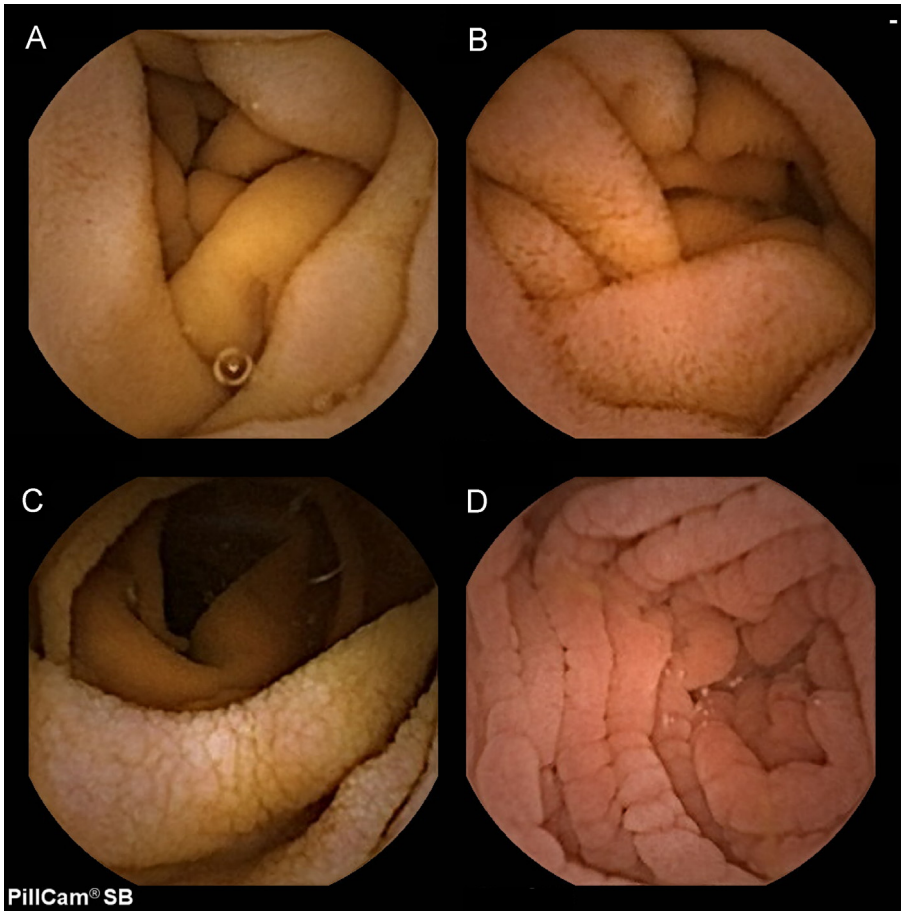

Fig. 1. Color videocapsule images obtained from the level of the duodenum. (A and B) Images from two control patients. (C and D) Images from two celiac patients. (For interpretation of the references to color in this figure legend, the reader is referred to the web version of this article.)

values rather than a few integer numbers. This would enable more precise classification and characterization of the patient health status. The system should also be automated. Such a system would involve software processing and analysis of endoscopic digital images, and those obtained by light microscopy. It should be adaptable to the changing presentation of the disease [22] as abnormality of the small intestinal mucosa can be time variable.

There are several potential advantages to implementation of an automated system as compared with manual image scoring and traditional biopsy evaluation. In bypassing manual rating and using automation, systems become easy to use, rapid, have low implementation and operational cost, do not require expert training, and eliminate user bias and therefore subjective results, with increased reproducibility. The speed for screening patients would be measureable in fractions of seconds, rather than many minutes or even hours as is needed to manually analyze the data from a single patient. Furthermore, the all-digital approach of these systems makes them efficient and readily integrated into hospital workflows, thereby presenting cost saving opportunities for health care providers. The long-term health implications of such a tool could potentially be enormous. It would be possible to detect subtle manifestations of the disease, as the detection resolution would be significantly greater as compared with the visual inspection and assessment of endoscopic images.

Automated quantitative systems potentially have several inherent disadvantages however, that should be considered during the design phase. First, the quantitative system may not reflect the optimal paradigm for detection of celiac disease and the presence of abnormality in the small intestine. Unless optimality can be achieved, there is the possibility of lowered sensitivity and specificity of the method. Second, a successful system will reduce the urgency for gastroenterologists to learn and retain skills for detection of any abnormality that may be present in endoscopic images. Third, if the system is hard-wired, there is no chance for machine learning to improve the paradigm based on new data. Fourth, there is currently a lack of software to distinguish the small bowel mucosa of healthy subjects from the mucosa of celiac patients where no pathology is apparent.

2. Designing an automated computerized system

To devise an automated system for gauging the degree of small intestinal abnormality from endoscopic images in suspected or known celiac patients will require the development of a paradigm that can proficiently detect and measure the abnormal aspects of the small intestinal mucosa that are relevant to celiac disease. Based on the modified Marsh score, this would include, but would not be limited to, the degree of crypt hyperplasia and villous atrophy, as well as the number of intraepithelial lymphocytes present. Currently, presence of villous atrophy is readily detected visually with high-resolution endoscopy [23]. Isolated lymphocyte infiltration of the mucosal layer without overt atrophy, however, is difficult to visualize even with high-resolution endoscopy [23]. Use of optical enhancement methods such as narrow-band imaging may also improve detection capability [23]. Thus improvement in detection methods will depend in part in enhancing the resolution and quality of the digital images obtained from both standard and videocapsule endoscopic techniques.

The analysis of intestinal villi, which have dimensions on the order of approximately one millimeter, is currently at the limit of resolution for both standard and videocapsule imaging systems [24]. Intestinal villi tend to become blunted in celiac patients and may even form clumps [25]. Such abnormal structures can become evident when using shape-from-shading principles to obtain a three-dimensional representation of a two-dimensional image [26,27]. When shape-from-shading is implemented, grayscale levels in two-dimensional images are transformed to linear or nonlinear distances, thereby creating a three-dimensional structure. A number of public domain shape-from-shading software algorithms are available for this purpose [28]. For more accurate three-dimensional reconstruction of the gastrointestinal tract, stereo-cameras that can simulate human binocular vision will be needed [28]. Associated features that are typically present in endoscopic images when there is villous atrophy including fissuring, a mottled or nodular appearance, and scalloping of the small intestinal folds [27]. These features can be detected and quantified computationally using a syntax [25]. Alternatively, two common statistical features that can be measured for comparison are the image mean brightness and the standard deviation in brightness [29]. It is likely that other textural measures will also be useful for comparisons, and therefore optimization criteria should be used to determine the best set of textural features for analysis.

Besides endoscopic data, digital images obtained from light microscopy slides can also be analyzed computationally and automatically. For example, measurement of the degree of curvature of intestinal villi provides a continuous, decimal number score for assessing villous atrophy [30]. The ratio of villous edge to piecewise arc length along the villi can be determined, and it is correlated to the Marsh classification of villous atrophy. To further the design of such systems, intestinal crypts should also be characterized, and similar metrics can be used. Other salient geometric measures that are useful for characterizing these abnormalities include the surface area and perimeter metrics. The extent of intraepithelial lymphocyte involvement in the intestinal mucosa can be measured either as a cell density with respect to other types of cells, or as a count of cells per unit area [31]. Color is an additional descriptor useful for characterization of cells observed in digital light microscopy slides. The incorporation of multiple descriptors such as these will be required for the development of automated systems that can detect any small bowel abnormality that may be present in celiac patients.

To integrate the aforementioned measurement methods for analysis, an automata-based polling technique can be implemented [26]. Automata are defined as a connection of functional nodes in a computerized network, and they are useful for quantitating physiological systems that include multiple salient features. At each node, a calculation is made based upon a set of equations and rules. For implementation in celiac disease analysis, each node should consist of a type of measured feature, which is then weighted by assigning a vote or a number of votes to the node. An example of a two-class quantitative and computational system would be one that automatically detects the presence versus absence of villous atrophy. In order to make an automated decision, at each node, the range of possible measurement values would be subdivided into those indicating the presence of versus lack of villous atrophy. This is analogous to subdividing the Marsh classification scheme into two classes: one class would consist of Marsh 0–II (no villous atrophy detected) while the other class would consist of Marsh IIIa–c (villous atrophy detected). Although such a subdivision for automated analysis would miss celiac patients with Marsh class I or II pathology of the small intestinal mucosa, it would provide a first step and has the advantage of simplicity. For each measured feature, a calculation is made and a vote or votes are assigned to its node. The features are polled, votes for all features are tallied, and the class with the most votes wins by simple majority. The image is thus characterized as being either one with presence or lack of villous atrophy. The paradigm is illustrated in Fig. 2. A digital image is acquired, and features of the image are detected. Each feature is then measured, and class is determined based upon the measurement value. A vote is assigned to the feature. Some features may be weighted by a single vote

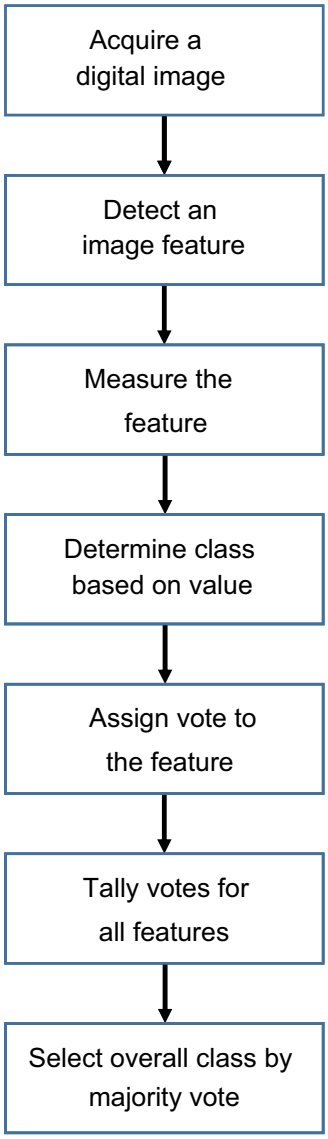

Fig. 2. Paradigm for automated polling to determine class. Using this paradigm, an image obtained during endoscopy or from biopsy slides can be classified automatically using quantitative features. Examples of classes are villous atrophy versus no villous atrophy.

while others may be weighted with multiple votes, depending on the importance of the feature, which is predetermined. Votes that have been assigned to all features are then tallied. The class is then selected to which the image belongs, for example, villous atrophy versus no villous atrophy, based upon majority vote.

The paradigm of Fig. 2 can be extended to multiple images or to an entire videoclip, with votes tallied for measurement from all images in the series. On a microscopic scale, the measurement area can be limited to image sectors, which are either constant or determined automatically based on a predefined textural or other feature analysis. This latter implementation would enable more precise detection and mapping of villous atrophy in areas where it is patchy. The paradigm for quantitative analysis can also be extended to involve additional classes. For example, classes could include no atrophy, versus Marsh IIIa, IIIb, and IIIc (four-class system).

The result of quantitative characterization would be useful to create a three-dimensional map of villous atrophy throughout the small intestine. This could be used for screening, as well as to correlate the presence and severity of villous atrophy with respect to other factors such as patient age and gender, estimated time in which the celiac patient went untreated, and degree of systemic involvement. The information would also potentially be of use to assist in determining the mechanisms governing the severity and location of villous atrophy, and whether these factors are time variant. For best results, analysis features should be optimized based on a set of criteria. Groundtruth could be for example the known Marsh score of a particular area of small intestinal involvement as determined by an expert pathologist from biopsy specimens. Similar paradigms could prove useful to computationally analyze both endoscopic and light microscopy images. For the light microscopy images, the additional features that should be quantitatively characterized are the measurement of crypts and intraepithelial lymphocytes.

3. Costs versus benefits

Implementation of automated quantitative methods will not eliminate the need for endoscopy and biopsies. Thus this additional evaluation will bring with it additional monetary costs, although they are likely to be minor. Furthermore, to devise such systems will require substantial effort to correlate each endoscopic finding with specific histopathology and then to automate it. However, the benefit of such systems would be to provide a more accurate assessment. Pathologic regions of the small intestinal mucosa caused by celiac disease are easily missed due to patchiness and subtlety. Moreover, presence of extraneous materials in endoscopic images including opaque fluids and air bubbles mask regions which may have pathology. Computerized methods can be of benefit when techniques to detect and mask extraneous materials appearing in the images are implemented so that these features are not included in the measurements done to detect pathology. A large series of endoscopic images require analysis in order to evaluate each patient suspected of having celiac disease [1,2]. Development of the automated methods would potentially reduce the time involved by alerting the analyst to areas which are most likely to have pathology. When the pathology is patchy, as is often the case [22], automated quantitation approaches will likely be of benefit to improve detection of suspicion areas in the duodenum and to target biopsies. A further benefit of automated quantitation would be to develop a means to differentiate celiac disease pathology of the small intestine from pathology due to other diseases. One way to approach this problem would be to determine ranges of quantitated feature parameters for each disorder and then to use discriminant function analysis to distinguish them.

4. Summary

Herein, suggested guidelines and focus areas for automating the detection of pathology in the small intestinal mucosa of celiac disease patients from endoscopic images have been described. The design and development of a computerized quantitative system for mapping abnormality in suspected or diagnosed celiac disease patients is a difficult task that will involve not only devising a set of features for characterizing the abnormality, but also determining the number of classes to be detected, selecting the best subset of features for classification, determining the weighting of each feature in terms of number of votes to be cast, and integrating the system into a computationally efficient software procedure [26]. The system should be adaptable so that it can be applicable for multiple class scenarios (for example, presence or lack of villous atrophy, as well as actual Marsh score) and so that it is useful for both macroscopic and microscopic mapping of pathologic regions. It should be adaptable for analyzing endoscopic images and also

digitized biopsy slide images, or a combined set of images. Implementation of any such system will involve relatively low costs since most of the work would involve software computer programming to analyze existing retrospective clinical data. There would be the possibility of significant benefit in terms of reduced time and financial costs for medical care, as well as for the improvement in public health, by earlier diagnosis of celiac disease, and by improved accuracy in the quantitative assessment of celiac patients.

Conflicts of interest statement

The authors have no conflicts of interest.

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