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EDITORIAL

Quantitative image analysis of celiac disease

Edward J Ciaccio, Govind Bhagat, Suzanne K Lewis, Peter H Green

Edward J Ciaccio, Govind Bhagat, Suzanne K Lewis, Peter H Green, Department of Medicine, Celiac Disease Center, Columbia University, New York, NY 10032, United States
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Correspondence to: Edward J Ciaccio, PhD, Department of Medicine, Celiac Disease Center, Columbia University, Harkness Pavilion 804, 180 Fort Washington Avenue, New York, NY 10032, United States. ciaccio@columbia.edu
Telephone: +1-212-3055447
Fax: +1-212-3420447
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Core tip: Celiac disease is quite common, being present in approximately 1% of the population worldwide. Although it is common, few cases are actually diagnosed because of the lack or screening and diagnostic tools. In this review we discuss currently used quantitative techniques and suggest directions for improved techniques. By using quantitative methods, it is possible to improve outcomes because these methods are automated, unbiased, rapid, and can detect low-level disease that is not evident by visual inspection of endoscopy images. Therefore, it may be possibly to more rapidly diagnose the disease to prevent morbidity by using computerized methods.

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Abstract

We outline the use of quantitative techniques that are currently used for analysis of celiac disease. Image processing techniques can be useful to statistically analyze the pixular data of endoscopic images that is acquired with standard or videocapsule endoscopy. It is shown how current techniques have evolved to become more useful for gastroenterologists who seek to understand celiac disease and to screen for it in suspected patients. New directions for focus in the development of methodology for diagnosis and treatment of this disease are suggested. It is evident that there are yet broad areas where there is potential to expand the use of quantitative techniques for improved analysis in suspected or known celiac disease patients.

INTRODUCTION

Celiac disease afflicts approximately 1% of the worldwide population, and there is no cure at present[1]. The patient, once diagnosed, must undergo a lifelong gluten free diet[2]. Gluten is a protein found in wheat, rye, and barley grains. An autoimmune response occurs when gluten is ingested by these patients[3]. The main location of the autoimmune response is the small intestinal mucosa[4]. The resulting immune cascade damages the small intestinal mucosa, particularly the proximal portions, *i.e.*, the duodenum and jejunum, but the ileum can be affected as well[5]. The villi which absorb nutrients can become short or blunted, and the mucosal alterations result in poor absorption of

nutrients[6]. Endoscopically, the mucosa shows fissuring and can have a mosaic appearance. However, not all patients show these features. The manifestations of the disease can be systemic as well and can affect neurological, endocrine, reproductive, hematologic, cardiovascular, and other systems, as well as lead to psychiatric issues[7,8].

Celiac disease is difficult to diagnose owing to the wide variety of symptoms in children and adults[9]. Patients may be suspected of having the disease if celiac serologies are positive[10]. Definitive diagnosis is currently established by endoscopy with biopsy of the small intestine[11]. Often, during standard endoscopy, four to six biopsies are obtained from the duodenum[12]. However, the atrophy may be subtle[13], and the current resolution of endoscopic imaging makes the endoscopic detection of villous atrophy difficult by visual observation alone. If villous atrophy is detected, the patient is put on a gluten-free diet[14]. If villous atrophy resolves the patient is confirmed as having celiac disease. Yet, a significant proportion of patients show no change or only slow and/or partial recovery of mucosal architecture (months or years) when put on the diet[15], and there may likewise be little or no change in serology[16]. It is unclear at present if the incomplete histologic and serologic recovery reflects continual, surreptitious ingestion of gluten in some individuals.

Recent efforts have concentrated on the possibility of using computer-assisted automated analysis to detect evidence of celiac disease in data obtained from endoscopic images of patients suspected of having celiac disease, and to monitor patients already known to have celiac disease. Although the standard endoscopy procedure is more commonly used to diagnose celiac disease, since 2004, videocapsule endoscopy has been available as an adjunct or alternative method for detecting abnormalities of the small intestine[17]. The videocapsule is swallowed by the patient and the camera adaptively obtains 2-6 image frames per second; however the camera angle and illumination with respect to the small intestinal wall is currently not controllable. Although it is mostly noninvasive and can reach all areas of the small intestine during transit through the gastrointestinal system, the images obtained using videocapsule endoscopy are also currently of lower resolution (576 × 576 pixels) than those obtained by standard endoscopy (up to 632 × 632 pixels). Recent efforts have focused attention on endoscopy images for automated computational analysis in the diagnosis and management of celiac disease[18,19], which will require the selection of satisfactory quantitative features for analysis.

QUANTITATIVE COMPUTERIZED METHODS

In active celiac disease villi become blunted (atrophied) and the indentations or crypts in the mucosa become elongated (hyperplastic). The Marsh score is used to determine the degree of villous atrophy semi-quantitatively[20]. A Marsh score of Ⅰ-Ⅱ suggests that there is no atrophy of the villi, however there is an isolated increase in intraepithelial lymphocytes or accompanying crypt hyperplasia of the small intestinal mucosa. A Marsh score of Ⅲa - Ⅲc indicates actual changes to the structure of the villi. On endoscopic examination of the small intestine of untreated celiac patients these changes result in fissuring in the small intestinal mucosa, a mosaic appearance, and scalloping of the small intestinal folds. All of these changes can be detected quantitatively in both standard and videocapsule endoscopy images. The advantage of using computational means is that there is no bias from one observer to the next, and subtle differences that may not be recognized by visual inspection can be detected. Furthermore, the computer program can be used to assign a quantitative real number score, which may be helpful for detecting celiac disease, which is often manifested as subtle changes in the small intestinal mucosa[21], and to more accurately monitor progress during treatment of the patients on a gluten-free diet.

Recent work has focused on using microscopic images to detect differences in mucosal architecture of celiac patients in areas of suspected villous atrophy, with respect to control patients who do not have villous atrophy. Initial work was done using standard light microscopic images of small intestinal biopsies to grade the degree of villous atrophy. The ratio of villous edge-to-piecewise arc length (E/P ratio) was calculated from light microscopy images[22]. It was found that the mean E/P ratio for Marsh Ⅲa patients was 2.76, while for Marsh Ⅲb it was 1.91, and for Marsh Ⅲc 1.18, with a significant difference between each class ($P < 0.001$). Furthermore, since a real-numbered score was obtained, there was no need to separate the patients into the classes Ⅲa, Ⅲb, and Ⅲc, as the E/P ratio itself provided the degree of atrophy on a real-number scale.

Using videocapsule images, it is possible, using textural measures, to distinguish areas of the small intestine with villous atrophy in celiac disease patients *vs* control patients without villous atrophy. Digital image texture is defined as a quantitative measure of the variability of the image pixels in terms of their brightness, color, or both. A simple textural measurement is the standard deviation or variance in pixel brightness over a specified image area. This measurement can be used in both standard and videocapsule endoscopy to distinguish areas of villous atrophy and other changes of the small intestine including fissuring and mottled appearance, *vs* a normal appearance of the small intestinal mucosa[23,24]. This metric makes sense intuitively - areas with pathology result in spatial variation in standard

endoscopy and videocapsule endoscopy images, resulting in a higher standard deviation. Whereas, when pathology is not present, the small intestinal mucosa is uniform, resulting in a lesser degree of standard deviation in pixel brightness.

Another measure of image texture is the degree of fissuring, which can be defined as the length L of mucosal fissures per unit area[25,26]. Using this measure in both standard and videocapsule endoscopy images, increasing L can be found for Marsh grades from Ⅱ, to Ⅲa, Ⅲb, and Ⅲc, respectively, in both types of images, with significant differences with respect to controls ($P < 0.001$). Frequency or spectral analysis has also been found useful for analysis[27]. The change in image mean over many image frames can be used to estimate the frequency spectrum, which is the degree of periodicity over time. If a pattern is repetitive over regular intervals it is said to be periodic. Furthermore, in celiac patients undergoing videocapsule endoscopy, there is a correlation between longer periodic components and greater textural magnitude[28]. Thus areas with greater pathology as measured by increased degree of texture in these patients tend to have longer periodicity in image frequency components, which may be related to lesser motility. Motility as measured by spatial fluctuations in the region of darkest pixels in videocapsule image series, estimated to correspond to the small intestinal lumen center, has been shown to be significantly less in celiacs *vs* controls[28].

More recent efforts to quantitate celiac disease mucosal abnormalities include the use of shape-from-shading in videocapsule endoscopy images to develop a three-dimensional map of the small intestinal mucosal surface[29]. Based on the shape-from-shading transform, the number of villous protrusions per image can be shown to be less in celiacs *vs* controls ($P < 0.001$), while the average protrusion width is greater in celiacs *vs* controls ($P = 0.01$), which may be related to blunting of villi compared to untreated celiac patients. For improved analysis, the aforementioned methods for quantitatively distinguishing celiac *vs* control images can be combined using an automated polling protocol or majority vote[30].

Recent quantitative work also includes potential solutions to highly difficult problems. A focus on scale invariance in the textural descriptors for celiac disease patients *vs* controls was done using the wavelet transform[31]. It is also possible to correct for endoscope distortion to improve mucosa-based classification of celiac disease in affected patches[32]. Highly discriminant Fourier filters can also be developed and applied for analysis[33]. This latter method was utilized for the automated classification of magnifying endoscope images with respect to duodenal imagery for the diagnosis of celiac disease. There is a high specificity for detection of mucosal pathology present in untreated celiac disease using this method.

Although standard and videocapsule endoscopy techniques are most commonly used for screening and analysis of celiac disease patients, enhanced imaging methods are becoming more accepted and utilized. These include i-scan technology, in which image texture, color, and tone are enhanced so that minute mucosal structures and subtle changes in color are more visually apparent[34]. Narrow-band imaging enables sharper visualization of mucosal structures by altering the light source with optical filters, particularly in the blue and green light bands[35].

Although automated diagnosis *via* the use of standard endoscopic imaging is not yet possible with good accuracy, methods in the spatial domain (histogram) and transform domain (wavelets) may provide the best classification results[36]. These methods have a relatively high specificity for detection of villous atrophy and other mucosal damage in celiac disease patients not yet on a gluten-free diet. For improved accuracy, methods of automated detection will need to overcome difficulties due to image distortion, varying texture orientation, and in developing a satisfactory multiclassifier[37].

Detection and measurement of villous atrophy in celiac disease patients including the extent of involvement, the correlation with clinical presentation, as well as the response to treatment are matters of continuing study[38]. Besides image analysis, additional measures of quantifying celiac disease associated mucosal alterations unrelated to imaging include the quantification of small intestine bacterial overgrowth from cultures of the intestinal aspirates in celiac disease[39]. It is also possible to quantitatively map T cell epitopes to more completely define antigenic peptides[40]. The peptides may change depending on whether gluten is present in the diet. Such studies will be important for the development of peptide-based therapeutics for celiac disease.

LIMITATIONS OF CURRENT METHODS

At the present time, lack of sufficient number of cases has been a factor in limiting the development of automated methods. Another difficulty is that maladies other than celiac disease can manifest as villous atrophy in the small intestine including giardiasis, collagenous sprue, immunodeficiency, autoimmune enteropathy, radiation enteritis, Whipple's disease, tuberculosis, tropical sprue, eosinophilic gastroenteritis, human immunodeficiency virus enteropathy, intestinal lymphoma, Zollinger-Ellison syndrome, Crohn's disease, and food intolerance. Distinguishing villous atrophy caused by any one of these disorders *vs* celiac disease requires further investigation. For patients who undergo videocapsule endoscopy without biopsy, there is a problem of confirmation of the presence of villous atrophy detected by image analysis, though serology may be helpful[41].

CONCLUSION

We conclude that recent methods to quantify pathologic features of the small intestinal mucosa in celiac patients, *vs* control patients lacking pathology, have been partially successful in improving the detection and description of such features. The problem can be defined as one of detecting regions with greater texture, and variable texture, in small intestinal mucosal endoscopy images *vs* normal images with uniform and slight textural magnitude, and slight changes in the difference of spatial magnitude. Development of appropriate descriptors, which include actual textural measures, but also frequency and three dimensional syntactic descriptors, can be useful to develop appropriate metrics, to discern differences in celiacs *vs* controls, and to define ranges in the degree of pathology in those patients with small intestinal abnormalities. Because the descriptors are quantitative, a real-numbered score is obtained that is not biased with respect to the human observer, and has the ability to computationally detect subtle differences, which may indicate celiac disease. Yet, computational quantitative methods can be biased in the sense that the choice of descriptors that are selected can be biased. Unless a performance index is used to optimize and validate the descriptors used, these quantitative methods may have limited usefulness and may only work for distinguishing certain types of images with pathology *vs* control images.

For optimum performance, future studies of the use of quantitative measures for detection of pathology in the endoscopic images of actual and suspected celiac disease patients should be robust to image characteristics and related to the precise level of the small intestine where it was obtained, the presence or absence of suspected areas of pathology, and camera angle and distance from the mucosal surface. Although correction and robustness for all of these variables may prove a formidable challenge, progress is being made that will lead to improved classification. As spatiotemporal resolution in the series of acquired images also improves, it may become possible to diagnose, or at least to confirm diagnosis, of celiac disease based on standard endoscopy or even videocapsule endoscopy images. Furthermore, it may also be possible to monitor adherence to the gluten-free diet in patients known to have celiac disease. A greater research effort is therefore recommended in the use of quantitative computational methods for characterization of the small intestinal mucosa in known and suspected celiac disease patients.

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