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REVIEW ARTICLE

Enhanced endoscopic imaging and gastroesophageal reflux disease

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Abstract Gastroesophageal reflux disease (GERD) and GERD-related symptoms are common, and affect 25% to 30% of the general population. Upper gastrointestinal endoscopy of the esophagus has been the most widely used modality for the diagnosis and grading of reflux disease. Endoscopic imaging today has evolved beyond the confines of routine white light endoscopy (WLE) to advanced optical imaging with a precise and real time endoscopic diagnosis. These technological advances have helped circumvent the limitation of WLE in reflux disease by a) improved detection of subtle irregularities, b) characterization of anomalies, and c) possible optical biopsies providing real-time diagnosis. This review attempts to define the current status of these newer technologies vis-a-vis the diagnosis and management of gastroesophageal reflux disease.

Keywords Barrett's esophagus · Esophagitis · White light endoscopy

Introduction

Gastroesophageal reflux disease (GERD) and GERD related symptoms are common affecting 25% to 30% of the general population in the West. Recent studies suggest a worldwide increase in prevalence of at least 4% per year [1]. The prevalence of symptoms of GERD occurring once a week, is approximately 8% [2] in Indian subjects. GERD causes a significant decrease in quality of life and is a huge economic burden as well [3, 4].

Upper gastrointestinal endoscopy and examination of the esophagus has been the most widely used modality for the diagnosis and grading of reflux disease [5]. However, there are two major limitations of conventional white light endoscopy (WLE) in the GERD spectrum.

A) **Non erosive reflux disease (NERD):** More than 60% of patients suffering from reflux symptoms show no visible changes on WLE [6]. Possibly, minute mucosal changes and minimal change esophagitis are not adequately visualized by conventional WLE [7, 8].

Consequently, NERD has remained a heterogeneous disease with reflux symptoms and an unpredictable response to antireflux therapy.

B) **Barrett's esophagus (BE) and surveillance**: There is an increasing worldwide prevalence of GERD together with a rising incidence of complications including BE and esophageal adenocarcinoma [9]. Early neoplastic lesions are difficult to diagnose with WLE. Four quadrant biopsies every 2-cm length is time-consuming, and has been associated with high sampling error. Moreover, the low incidence (0.5% per year) reduces the cost effectiveness of this laborious surveillance measure [9–11].

Endoscopic imaging today has evolved beyond the confines of WLE to advanced optical imaging with a precise and real time endoscopic diagnosis [12] (Fig. 1a and b). These technological advances have helped circumvent the limitation of WLE in reflux disease by a) improved detection of subtle irregulari-

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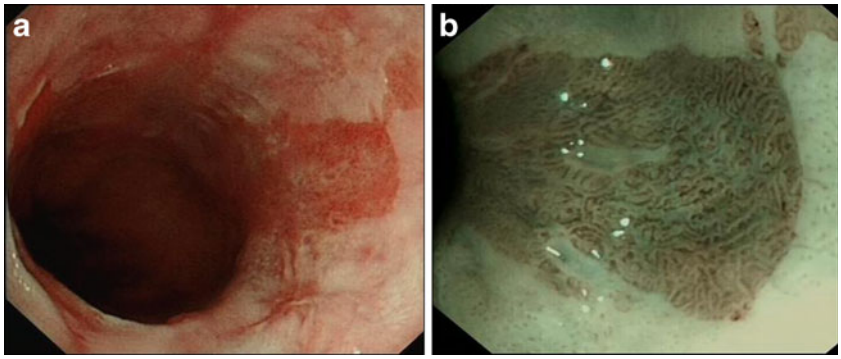

Fig. 1 **a** Barrett's esophagus on WLE. **b** On NBI, a ridged pit pattern with regular vascular pattern clearly identified

ties and b) characterization of anomalies and possible optical biopsies providing real time diagnosis.

Newer imaging technologies in GERD

Newer imaging technologies used in GERD can be categorized into:

I) Image enhanced endoscopy (field enhancement) technologies

These allow enhanced recognition and characterization of vessel and tissue architecture of the entire field, and include.

i) High resolution magnification endoscopy (HRME)
ii) Contrast enhancement using dye (chromoendoscopy)
iii) Digital chromoendoscopy including narrow band imaging (NBI), I scan and Fuji Intelligent Chromo Endoscopy (FICE)
iv) Autofluorescence endoscopy.

II) Virtual histology or point enhancement technologies

These allow in vivo virtual histological examination during endoscopy and include:

i) Confocal laser endomicroscopy (CLE)
ii) Optical coherence tomography (OCT)

III) Newer technologies: spectroscopy, molecular imaging

I) Image enhanced endoscopy (field enhancement)

(i) High resolution magnification endoscopy

HRME involves the use of high resolution endoscopes of around 850K pixel density with a movable lens and optical zooming facility of up to × 200 magnification. This results in a higher resolution magnified image with the ability to detect and discriminate minute lesions [13].

HRME has been able to identify subtle changes, such as punctuate erythema, pinpoint vessels and triangular indentations above the Z line (GE junction) in subjects with otherwise normal WLE [7].

A few studies have evaluated these changes as markers of minimal change esophagitis in NERD [14]. Kiesslich et al. demonstrated endoscopic signs of minimal change esophagitis for the prediction of NERD in 39 patients before and after treatment with esomeprazole [15]. In a small pilot study of 18 patients, we found subtle vascular pattern changes including the comma-shaped intrapapillary capillary loops in subjects with NERD, which resolved after PPI therapy.

HRME was also used initially for detection of BE [16, 17]. Subsequently, for the characterization of BE, HRME alone has not been much reported. However, increased detection rates of high-grade dysplasia (HGD) have been with HRME together with indigo carmine dye spraying or NBI [18].

The primary limitation of magnification endoscopy has been a substantial inter and intra observer variability with unacceptable kappa levels. The advent of newer generation endoscopes including NBI with greater contrast enhancement has helped define and categorize the changes of both minimal change esophagitis and BE.

(ii) Contrast enhancement using dye (chromoendoscopy)

Chromoendoscopy involves the topical application of dyes for image enhancement during endoscopy. Vital stains, which actively stain the cells, and contrast stains, which are not absorbed but pool in the crevasses of the mucosa are used. Of these, Lugol's iodine, methylene blue and indigocarmine are the most commonly used for the esophagus [13].

Lugol's iodine has been used to detect minimal mucosal breaks and identify minimal change esophagitis in a subset of patients with NERD. Iodine is absorbed by the glycogen containing non-keratinized squamous epithelium and stains the normal esophagus. Inflammatory or dysplastic squamous

epitheliums do not stain and appear as unstained streaks [19].

Methylene blue and indigocarmine spraying on the other hand has primarily been used to characterize BE [20, 21]. Five distinct patterns of columnar-appearing mucosa have been described including small/round, straight, long oval, tubular and villous patterns. Metaplastic tissue has been associated with tubular and villous patterns in various reports. The overall results of chromoendoscopy for the diagnosis of dysplasia in BE have been inconsistent [20, 21]. However, there has been a consistent and significant reduction in the number of biopsies required for diagnosis [18, 21].

Overall, chromoendoscopy has limited usage in GERD and BE in view of inconsistent results, possible DNA effects of the vital dyes, inability to detect superficial vascular patterns and of course the time consuming and messy procedure. The advent of the no-dye "switch of the button" digital chromoendoscopy appears a promising alternative to chromoendoscopy [22–24].

(iii) Digital chromoendoscopy (NBI/I scan/FICE)

Digital chromoendoscopy has been developed as an alternative method of visual enhancement similar to chromoendoscopy. These novel optical technologies include NBI, I scan and FICE, which can demonstrate and distinguish the alteration in the pit pattern and vasculature between inflammatory and neoplastic lesions [25].

Narrow band imaging (NBI)

NBI developed by Olympus Medical Systems (Olympus, Japan) is the most well-recognized advance in endoscopic imaging. This involves the placement of narrow band pass filters to obtain tissue illumination at selected narrow wavelength bands enhancing visualization and assisting in tissue characterization, differentiation and diagnosis.

Normal esophagus on NBI

On NBI, the stratified squamous epithelium of the esophagus appears featureless and has no pit pattern. There is a regular pallisading capillary network. The limit between the squamous and columnar epithelium (CLE) is clearly demarcated. The intra papillary capillary loop (IPCL) pattern, which is barely visible on WLE is clearly outlined on NBI. The normal IPCL is a smooth running small diameter capillary vessel positioned upright from a branching vessel about 10 μm in size. The branching vessels appear green while the IPCLs are observed as dark brown loops/dots on NBI [26].

IPCLs have shown characteristic changes including dilatation, prolongation, meandering and irregularity in form and caliber according to the extent of tissue atypism from inflammation to dysplasia and cancer. Many of these publications are in Japanese. Inoue et al. have actually classified IPCLs from Type I (normal), Type II (inflammation), Type III (borderline), Type IV (carcinoma in situ) to Type V (invasive CA) [26, 27]. IPCL pattern analysis, thus, assists in the diagnosis of GERD and related complications [25].

NBI in GERD and NERD

Conventional WLE has often been considered to be a relatively insensitive test for GERD because it is able to identify lesions in only 40% of cases with symptoms (NERD) [28]. The ability of NBI to depict subtle mucosal lesions has improved the diagnostic accuracy.

Various subtle changes not seen regularly on WLE have been noted on NBI. These have included a) increased Type II IPCLs (elongated and arranged in linear orientation) above the Z line b) punctate erythema proximal to the Z line c) increased vascular markings distal to the Z line d) triangular indentations of columnar mucosa at the SC junction and e) islands of squamous epithelium distal to the Z line [29, 30]. Some of these changes have been found to be reversible on PPI therapy and may represent the true endoscopic markers of minimal change esophagitis [29, 31].

Sharma et al. in their landmark study of 80 patients with GERD reported an increased number and dilatation of IPCLs as the best predictors of GERD on multivariate analysis. The number of IPCLs per field was higher in GERD. Also a higher proportion of patients with GERD had changes in the number (OR 12.6; $p>0.00001$), dilatation (OR 20; $p>0.0001$) and tortuosity (OR6.9; $p>0.001$) of IPCLs [32]. Similarly, we evaluated 60 patients with NERD on WLE by NBI [29]. Minimal changes were detected in 21 patients. Increased and dilated IPCLs were noted most frequently in 19/21 (90.4%) patients. Increased vascular markings with hyperemia and punctate erythema proximal to the Z line was detected in 15/21 (71.4%). Interestingly, these resolved in 95% cases on PPI therapy. Fock et al. in a recent study of 107 subjects used simpler criteria including microerosions, increased vascularity and pit pattern at the GE junction to identify minimal change disease with good interobserver agreement [30].

The subset of NERD subjects with minimal changes on NBI responds better to PPI. Accordingly, NBI may used for prediction of therapeutic response to PPI in NERD [29, 31]. The ability of NBI to detect small erosive foci could also increase consistency in the grading of erosive disease (GERD). In a recent comparative study of endoscopic images of 230 patients by WLE and NBI, both intra and

interobserver reproducibility in grading esophagitis was improved with NBI (kappa 0.62 vs. 0.45) [33].

On NBI, inflamed mucosal breaks appear dark brown (crowding of capillaries). The classical appearance of minimal change esophagitis on NBI is found in a subset of patients with normal appearing mucosa on WLE (Fig. 2a and b). This includes a central fine ridge above the Z line with plenty of dilated intrapapillary capillary loops (IPCLs) arranged in a linear fashion giving an "inverted fir tree" appearance, which resolves on PPI therapy [34].

There are still some limitations on the routine use of these endoscopic criteria in clinical practice. The assessment of dilated and tortuous IPCLs could be subjective, and objective manual counting of IPCLs is time-consuming and complicated as only a small area can be seen at one time.

NBI endoscopy in Barrett's esophagus

BE is a known premalignant lesion; the increasing prevalence of esophageal adenocarcinoma has been attributed to the increasing incidence of GERD and BE especially in the western world. Accordingly, regular surveillance of BE with random four quadrant biopsies every 1–2 cm has been the standard practice. However, the distribution of dysplasia within BE is patchy and not clearly visible with WLE. The random biopsy technique is, thus, suboptimal and subject to sampling error.

The role of NBI in detection of esoBE and early cancer has been evaluated in quite a number of studies. A spectrum of changes from CLE to HGD and malignancy has been described (Fig. 3a and b).

Kara et al. classified Barrett's according to the mucosal pattern (flat, villous/gyrus, irregular), vascular pattern (regular, irregular, long branched) and the presence of abnormal blood vessels. Intestinal metaplasia was associated with the villous/gyrus patterns in 80% cases and a flat mucosa in 20% of cases. On the other hand, HGD was characterized by irregular/disrupted mucosal and vascular patterns with abnormal blood vessels [35].

Sharma et al. used a simplified version with using mucosal (ridged/villous, regular, irregular) and vascular (normal and abnormal) patterns. Here, the ridged/villous pattern had a sensitivity, specificity and PPV of 93.5%, 85% and 94.7%, respectively for the diagnosis of specialized intestinal metaplasia (SIM). The distorted vascular pattern had a sensitivity and specificity of 100% and 98.7%, respectively [36].

Goda et al. on the other hand, used a more elaborate classification of the mucosal patterns into round/oval, long straight, villous, cerebriform and irregular and vasculature into honeycomb, vine like, coiled, ivy like and irregular [37].

Singh et al. have recently proposed a combined classification based on both the mucosal and vascular pattern i) Pattern A: round pits and regular vasculature ii) Pattern B: villous/ridged pits and regular vasculature iii) Pattern C: absent pits but regular microvasculature and iv) Pattern D: distorted pits with irregular microvasculature. Pattern A had a high PPV (100%) and NPV (97%) for CLE without SIM. Patterns B and C were indicative of SIM. Pattern D had a PPV and NPV of 81% and 99%, respectively for HGD [38].

A recent meta analyses assessed the accuracy of NBI for the characterization of dysplasia in BE with histopathology. Four hundred and forty-six patients with 2,194 lesions were assessed. It revealed a high diagnostic precision for HGD with a pooled sensitivity, specificity, diagnostic accuracy and AUC of 0.95 (95%CI 0.87–1.0), 0.65 (95% CI 0.52–0.78), 37.53 (95% CI 6.50–217.62) and 0.88 (SE 0.08), respectively. NBI was also able to characterize SIM with high sensitivity but the specificity was poor [39].

Head to head comparative studies of NBI vs. conventional WLE in BE have assessed sensitivity, specificity, diagnostic accuracy and image quality.

Hammamoto et al. reported improved visualization with NBI using a scoring system of 0–4 to grade the quality of images. The squalmo-columnar junction was visualized with a score of >3 in 57% of NBI compared to 17% with WLE (p=0.0002). The blood vessel and CLE observation was also higher with NBI (100% vs. 80%) [40]. Curvers et al. also reported significantly better image quality with NBI

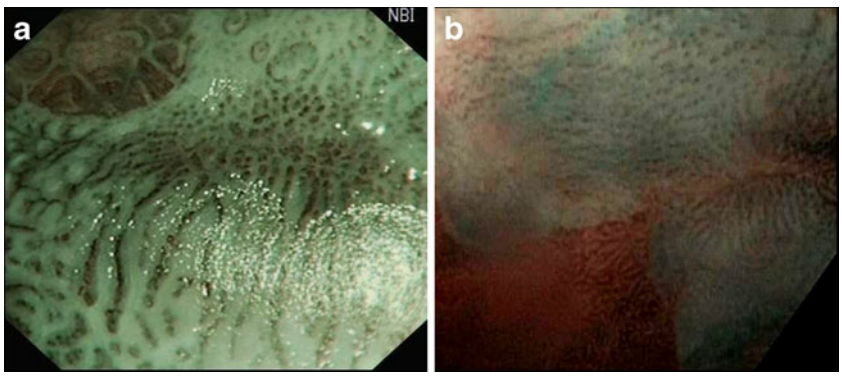

Fig. 2 a,b Typical appearance of minimal change esophagitis with dilated IPCLs arranged in a linear fashion (inverted fir tree). WLE was normal

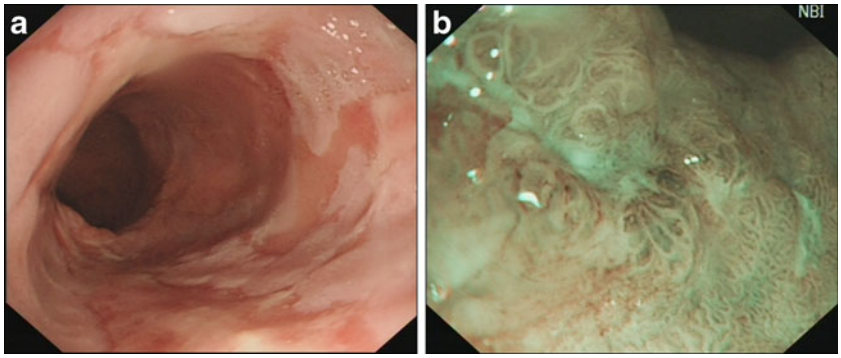

Fig. 3 **a** Long segment Barrett's esophagus on WLE. **b** BI with magnification shows a focal area of non parallel irregular pit pattern with few irregular microvessels. Targeted biopsy showed moderate grade dysplasia

compared to WLE (11.3 vs. 10.9 on visual analog scale; $p=0.01$) but the diagnostic yield of neoplasia did not improve (81% vs. 83%) [41]. A recent study by Singh et al. had reported a significant difference in the detection of HGD with NBI (95% vs. 62.5%; $p<0.006$) [42].

We find a majority of studies comparing NBI with WLE and other modalities appear favourable for NBI. The primary advantage of NBI is the detection of advanced dysplasia using fewer biopsy samples compared to surveillance WLE and four quadrant biopsy. Wolfsen et al. reported 57% detection of dysplasia compared with 43% with conventional WLE and random biopsies. Additionally, the number of biopsy specimens in the four quadrant group was much higher than targeted with NBI (mean 8.5 vs. 4.7) [43]. However, some interobserver studies have questioned the additional value of NBI for detection of high grade dysplasia. Also NBI does appear to be operator experience dependant and a recent study found NBI to be of limited value in BE with endoscopists in general practice [44].

Feasibility of FICE/I scan for the diagnosis of GERD

I scan (Pentax, Montvale, NJ, USA) and FICE (Fujinon, Wayne, NJ, USA) involve spectral estimation technology and are based on post imaging processing. There is no optical filter involved in contrast to NBI. These post processing systems have been recently evaluated for the detection of mucosal breaks in GERD.

In a study of 50 patients with reflux symptoms, the detection rates of mucosal lesions improved with I scan. The degree of esophagitis could be upgraded in 10% cases [45]. A similar small study with FICE has shown higher sensitivity, NPV and accuracy than WLE. However, the interobserver agreement was poor [46].

Autofluorescence endoscopy

Autofluorescence imaging (AFI) is based on the detection of the relative concentration of endogenous fluorophores and fluorescence emission between healthy and neoplastic tissue. The use of AFI in GERD is primarily as a wide area functional imaging of Barrett's mucosa for identification of dysplastic areas [47].

A few studies have shown improved detection of HGD and detection of additional cases on AFL compared to WLE with four quadrant biopsies. The sensitivity and PPV, however, are poor with unacceptably high false positives [48]. As such the role of AFI as a standalone technique for BE appears remote.

Endoscopic trimodal imaging (ETMI)

The ETMI system (Olympus, Tokyo, Japan) incorporates high resolution WLE together with AFI and NBI modalities, which can be used in tandem. The improved sensitivity and specificity of the combined technique is primarily attributable to reduction of the false positivity of AFI [47]. This has been the primary intention of the studies of trimodal imaging in BE. Kara et al. first reported a significant reduction of false positive AFI with trimodal imaging [49]. In a similar multicentre trial, Curvers et al. found that AFI could identify all cases with HGD and false positivity was reduced by NBI from 81% to 26% [50]. The same group has recently reported improved detection of early neoplasia with ETMI compared to WLE. Here again, NBI reduced the false positivity of AFI but did misclassify 17% of cases [51].

Very interestingly, the results were not repeated when the procedures were performed by general endoscopists in the community setting and the detection of dysplasia did not improve with ETMI [45].

II) Virtual histology/optical biopsy

(i) Confocal laser endomicroscopy (CLE)

CLE allows subsurface analysis of the gastrointestinal mucosa using the principle of optical sectioning. This enables real time in vivo histology during ongoing

endoscopy. The current CLE incorporates a confocal laser microscope into the tip of a flexible endoscope (Pentax EC 3830FK, Tokyo, Japan). A probe based confocal endomicroscope (Cellvizio, Mauna Kea technologies, France) is also available.

There is limited full length publications on the use of CLE in BE but numerous abstracts have been presented [52]. Becker et al. reported significantly higher microvessel density in neoplastic BE compared to non-neoplastic lesions (23.6% vs. 14.2%; $p>0.001$) on CLE [53]. Kiesslich et al. in a study of 63 patients with BE demonstrated good correlation between in vivo histology and conventional histology in normal squamous vis-a-vis gastric and Barrett's epithelium. A confocal classification system to predict the histopathology of the distal esophagus was also proposed. Non dysplastic BE was characterized by regular villous like epithelium with dark goblet cells. An increase in the number of dark cells with an irregular border was consistent with BE associated neoplasia. The loss of regular basement membrane integrity and disruption of the villous epithelial structure suggested HGD/CA [54].

As with new technologies, CLE would need time for move from the research arena into routine clinical practice [55]. However, initial results for the prediction of dysplasia in Barrett's lesions in real time are promising [56].

(ii) Optical coherence tomography (OCT)

OCT is a recent imaging modality being developed as a potentially valuable method for high-resolution cross-sectional imaging of the esophageal mucosal and submucosal layer. It takes advantage of the short coherence length of broadband light sources to perform cross-sectional imaging of tissue enabling non invasive, in vivo optical biopsy. OCT provides the highest resolution of the technologies currently available in endoscopic imaging [57].

Studies with gastrointestinal OCT have primarily focused on BE and the identification of dysplasia. OCT has also been used to identify the subsquamous Barrett's epithelium in patients who have undergone ablative therapy, which is not visible on standard endoscopic examination [58].

Currently, preliminary clinical studies have shown impressive results. However, larger prospective trials are needed before OCT enters routine clinical practice.

III) Newer imaging advancements [59, 60]

Spectroscopic techniques, such as light scattering spectroscopy and Raman spectroscopy carry diagnostic information on the microstructural and molecular composition of tissues, which enable early detection of dysplasia. Similarly, peptides have been used as molecular probes that can be fluorescence tagged and identify cell surface targets/molecular markers of neoplasia in BE. The results are promising. However, these novel technologies are very much in the experimental stage and beyond the scope of this review.

Conclusion

Improved detection of GERD and surveillance of BE have now become essential in the background of rising incidence worldwide. The available research on the enhanced imaging technology appears promising. NBI has been evaluated extensively and appears to be a useful adjunct to WLE for identification of minimal change esophagitis and for the targeted investigation of suspicious areas in BE. There is considerable evidence that NBI would help target endoscopic biopsies and delineate resection margins during endotherapy of dysplastic areas. The days of random four quadrant biopsies may well be over.

The primary limitation as with all new technologies is the lack of sufficiently validated and standardized classification systems and the limited number of randomized controlled trials. Additionally, most of these are conducted at tertiary care specialized centres. Routine clinical practice and cost effectiveness remain to be tested or achieved.

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