NONEROSIVE REFLUX DISEASE : COMPARATIVE ANALYSIS OF SYMPTOMS SEVERITY, ENDOSCOPIC AND 24-HOURS PH-IMPEDANCE

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LIST OF ABBREVIATIONS

AET	**Acid exposure time**
BMI	**Body mass index**
EoE	**Eosinophilic esophagitis**
ERD	**Erosive reflux disease**
GERD	**Gastroesophegial reflux disease**
NERD	**Nonerosive reflux disease**
PPI	**Proton pump inhibitor**
SAP	**Symptom associated probability**
SI	**Symptom index**

ABSTRACT (ENGLISH)

NON-EROSIVE REFLUX DISEASE : COMPARATIVE ANALYSIS OF SYMPTOMS SEVERITY, ENDOSCOPIC AND 24-HOURS PH IMPEDANCE

Background : Non-erosive reflux disease (NERD) has emerged as a real entity in the spectrum of gastroesophageal reflux disease (GERD) and may, indeed, represent the most common manifestation of reflux disease. NERD is defined as presence of troublesome reflux symptoms and the absence of mucosal breaks at endoscopy.There are many studies done regarding NERD, but none of the study looks into the symptom severity , endoscopic and 24-hours pH-impedance monitoring. Our aim is to compare the symptom score with endoscopic and pH-impedance monitoring with the endoscopic findings.

Methodology : This was a prospective study of patients presenting with various upper gastrointestinal symptoms between 1st June until 30th November 2014. From all, patients with nonerosive reflux disease were included after the upper endocopy (excluding erosive reflux disease) and multiple esophageal biopsies were taken from multiple level of oesophagus. From all the NERD patients, 24-hours ambulatory pH-impedance monitoring will be done in all consented patients.

Results : From this study, we conclude that the severity score for dysphagia (p value 0.003), the possibility for esophageal changes observed from upper gastrointestinal endoscopy were expected. A total of 28 NERD participants underwent 24-hour pH studies. The median (IQR) DeMeester score was 4.94 (11.90) but none of the endoscopic findings were expected in positive pH study in NERD population. We also found 3 patients with eosinophilic esophagitis with prevalence of 3.6%.

Conclusion : The study showed a significant association between symptom score for dysphagia, with positive endoscopic (esophagitis) findings , and there were no association between endoscopic changes in positive pH study in NERD population.

ABSTRAK (BAHASA MELAYU)

Latar Belakang

Penyakit refluks yang bukan menyebabkan hakisan (NERD) telah muncul sebagai satu entiti sebenar dalam spektrum penyakit refluks gastroesophageal dan sesungguhnya, mewakili manifestasi yang paling biasa dalam penyakit refluks. NERD didefinisikan sebagai kehadiran simptom refluks dan tiada keterasingan mukosa sewaktu endoskopi.Terdapat banyak kajian yang telah dijalankan berkaitan penyakit refluks ini, tetapi tiada satu pun daripada kajian sebelum ini melihat kepada keterukan gejala, endoskopi dan pemonitoran pH-impedance selama 24 jam. Matlamat kami adalah untuk membandingkan skor gejala dengan endoskopi dan pemonitoran pH-impedance dengan ciri-ciri endoskopi.

Metodologi

In adalah satu kajian prospektif melibatkan pesakit yang mengalami pelbagai simtom yang melibatkan bahagian atas trek gastrousus daripada 1 Jun 2014 sehingga 30 November 2014. Daripada semua pesakit , cuma pesakit yang mempunyai normal esofagus selepas menjalani endoskopi terhadap trek atas gastrousus telah dimasukkan sebagai subjek dan beberapa biopsy terhadap esophageal telah diambil dari pelbagai sudut. Daripada semua subjek berkenaan, cuma yang memberi keizinan yang akan menjalani pemonitoran “pH-impedance “ secara 24 jam ambulatori.

Keputusan

Daripada kajian ini, kemungkinan untuk mengalami perubahan esophageal yang diperhatikan melalui endoskopi trek gastrousus, dijangkakan untuk skor keterukan yang melibatkan simtom disfagia (nilai p 0.003). Seramai 28 orang pesakit NERD melalui ujian “pH-impedance” secara 24 jam ambulatori. Median (IQR) bagi markah DeMeester ialah 4.94 (11.90) tetapi tiada sebarang penemuan endoskopik dijangkakkan untuk kajian pH positif dalam populasi pesakit yang mengalami penyakit refluks yang bukan menyebabkan hakisan (NERD). Hasil daripada kajian ini juga mendapati bahawa prevalensi untuk esofagitis esinofilik adalah 3.6% iaitu ditemui dalam 3 orang pesakit.

Kesimpulan:

Hasil kajian ini menunjukkan terdapat perkaitan yang signifikan antara skor simtom untuk disfagia dengan ciri-ciri endoskopik yang positif dan tiada perubahan endoskopi dijangkakan dalam kajian pH yang positif dalam populasi pesakit yang mengalami penyakit refluks gastrousus yang bukan menyebabkan hakisan (NERD).

1.INTRODUCTION

1.1 Background of GERD,NERD and EoE.

Gastroesophageal reflux disease (GERD) is highly prevalent worldwide and represents an important medical problem in Western countries (Armstrong, 2008). And about two thirds of individuals affected by gastroesophageal reflux disease suffer from endoscopy-negative reflux disease(Vieth, 2007).

GERD encompasses a wide spectrum of clinical manifestations , ranging from symptoms with anatomical lesions (erosive esophagitis / erosive reflux disease = ERD) , symptoms without anatomical lesions (nonerosive reflux disease = NERD) and complications such as ulcers, strictures, haemorrhage, and Barrett's esophagus(Locke *et al.*, 1997). The term of "esophagitis" currently refers to endoscopic alterations (mucosal breaks)(El-Serag and Sonnenberg, 1998) that are classified on the basis of their extend(Armstrong *et al.*, 1996).

Nonerosive reflux disease (NERD) is a distinct pattern of gastroesophageal reflux disease (GERD). It has been observed that most of the community-based GERD patients appear to have NERD (Chen and Hsu, 2013b). Indeed, it is now clear that that nonerosive reflux disease(NERD) , may account up to 70% of patients with GERD in the community(Lind *et al.*, 1997; Smout, 1997) . In clinical practice, patients with reflux symptoms and negative endoscopic findings are markedly heterogeneous(Fass, 2007)

About 20% of the population in Western countries complain of experiencing typical symptoms of the disease (heartburn and acid regurgitation) and is the most common disease in patients referred for upper endoscopy. The incidence of GERD is probably underestimated, because many patients present with extraesophageal symptoms such as cough, hoarseness of voice and chest pain(Armstrong, 2008) .Reflux-related symptoms and lesions do not necessary coexist, given that about 30% to 70% of patients who complain of typical GERD symptoms have no sign of esophagitis based on endoscopy (NERD)(Armstrong, 2008).

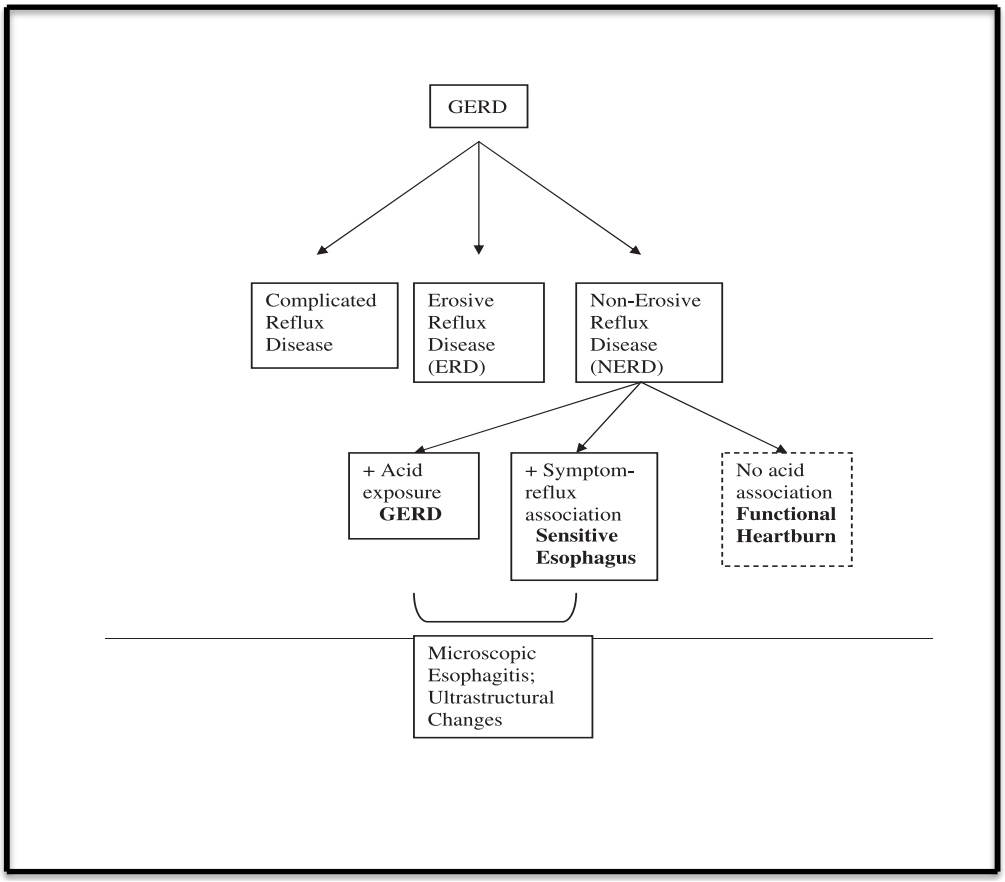

Figure 1. GERD subgroups.

Source from ： (QUIGLEY, 2006)

Eosinophilic esophagitis (EoE) is characterized by eosinophilic infiltration of the esophageal mucosa potentially related to an antigen-driven immunologic process (Fornari , Wagner et al. 2012) and results in clinical sign and symptoms, and endoscopic findings that may be indistinguishable or overlap with those of gastroesophageal reflux disease (GERD)(Noel and Tipnis, 2006) . It was first described as 'idiopathic EoE', 'primary EoE', 'allergic esophagitis', 'corrugated esophagus' in varying detail.

Eosinophilic esophagitis (EoE) is a clinicopathologic disease characterized clinically by symptoms related to esophageal dysfunction and pathologically by eosinophil-predominant inflammation in one or more biopsy specimens(Straumann, 2008). It is an emerging under-diagnosed, chronic clinical entity with increasing prevalence over the last decade, which affects children and adults. EoE also noted to be increasingly common diagnosis among patients with refractory gastroesophageal reflux disease (GERD) (Foroutan *et al.*, 2010).

1.2 Definition of GERD,NERD and EoE.

Gastroesophageal reflux disease (GERD) is defined by the American College of Gastroenterology as symptoms or mucosal damage produced by the abnormal reflux of gastric contents into the esophagus(DeVault *et al.*, 1999) and has been defined in the Montreal Consensus Report as a chronic condition that develops when the reflux of gastric contents into the esophagus in significant quantities causes troublesome symptoms with or without mucosal erosions and/or relevant complications(Vakil *et al.*, 2006).

Nonerosive reflux disease (NERD) is defined as "the presence of troublesome reflux-associated symptoms and the absence of mucosal breaks at endoscopy" according to the Montreal definition(Joh *et al.*, 2007). NERD was then defined as a subcategory of GERD by The Vevey Consensus Group, characterized by troublesome reflux-related symptoms in the absence of esophageal erosions or breaks at conventional endoscopy and without recent acid-suppressive therapy.(Modlin *et al.*, 2009).

NERD is not a homogenous disorder and incorporates subgroups which differ significantly in terms of presentation, pathophysiology and management. Studies have shown that about 30-50% of NERD patients demonstrate esophageal acid exposure within the physiological range(Martinez *et al.*, 2003).

Fass an colleagues have suggested that NERD may be further defined and subclassified, based on the results of 24-h pH recordings, into three distinct groups(Fass *et al.*, 2001). (Figure 1) :

1. Those with an abnormal acid exposure time (AET). These individuals appear to behave, in terms of therapeutic response, in a manner analogous to those with obvious esophagitis.

2. Those who demonstrate a normal AET but in whom symptoms and reflux events are significantly correlated (as estimated by some form of symptom index or other measure of symptom–reflux event association). These individuals have been referred to as having 'the sensitive esophagus'(Watson *et al.*, 1997) .

3. Those with typical reflux symptoms (i.e., heartburn and/or acid regurgitation), yet in whom all parameters of the pH study are normal. These individuals appear highly resistant to acid-suppressive therapy (Watson *et al.*, 1997), their symptoms commonly overlap with other functional disorders such as irritable bowel syndrome and functional dyspepsia, and they are more likely to demonstrate psychopathology. This group is best described as experiencing functional heartburn(QUIGLEY, 2006).

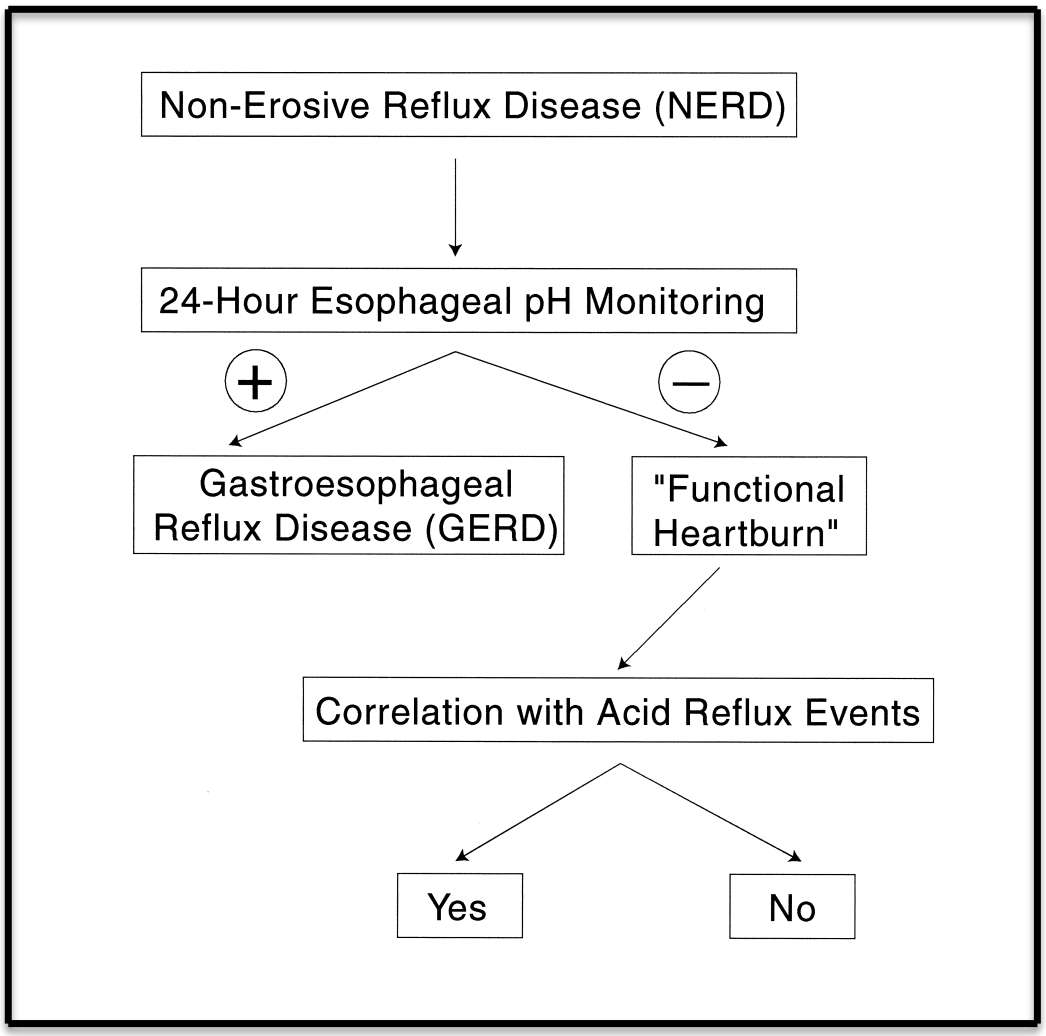

Figure 2. Subcategorization of the nonerosive reflux disease (NERD) group by using 24-h esophageal pH monitoring and “symptom index,”

Source from : (Drossman, 1999)

Eosinophilic esophagitis (EoE) is defined by Consensus Report(Furuta *et al.*, 2007) and 2011 update (Liacouras *et al.*, 2011)based on general symptoms and signs of esophagitis, ruling out gastroesophageal reflux disease(GERD) , and peak eosinophils count on biopsy (≥ 15 eosinophils per maximally affected high-power field [HPF])(Mulder *et al.*, 2013).

Consensus recommendations have recently been made by the First International Gastrointestinal Eosinophil Research Symposium (FIGERS) subcommittees (Furuta *et al.*, 2007), which define EoE with three statements:

(1) Symptoms including, but not restricted to food impaction and dysphagia in adults, and feeding intolerance and GERD symptoms in children;

(2) 15 or more eosinophils/HPF;

(3) Exclusion of other disorders associated with similar clinical, histological or endoscopic features, especially GERD, with PPI treatment or esophageal pH monitoring.

1.3 Prevalence of NERD

. Early studies reported that about 50% of patients with heartburn were found to exhibit normal esophageal mucosa during endoscopy. Previous studies showed that the prevalence of NERD is therefore estimated to be between 50% and 70% of the GERD population in western countries. (Gonsalves and Kahrilas, 2009). However, several recent community-based European studies of NERD patients found a much higher prevalence of 70% (Liacouras *et al.*, 2005).

. Other international studies on subjects in primary care centers showed that about 50% of their enrolled patients had normal upper endoscopy(Carlsson *et al.*, 1998). A US study on subjects who had their reflux symptoms controlled by antacids alone has shown that 53% of those subjects had no erosive esophagitis on upper endoscopy(NERD) (Robinson *et al.*, 1998).

. In Japan, recent reports described a prevalence of approximately 85%, which is considered higher than that in Scandinavian countries and the USA. The reasons for these variations are unknown (Miwa *et al.*, 2004). In Asian studies ,Wu *et al.* (Wu *et al.*, 2002) recorded a prevalence of 46.7% and another study by Rosaida *et al.*(Rosaida and Goh, 2004) reported a prevalence of NERD of 65.5% in multiracial Asian population.

1.4 Epidemiology of NERD

While gender and age are by no means absolute discriminators for any group of GERD, it is noteworthy that, in NERD, a group who, on the whole , tend to be younger , by a factor of about a decade, than in patients with erosive reflux disease (ERD)(QUIGLEY, 2006). Likewise, the patients with nonerosive reflux disease (NERD) are more often thinner (low body mass index) than those with erosive reflux disease (ERD) and more likely to be female (Venables *et al.*, 1997; Carlsson *et al.*, 1998). A body mass index of less than 24 kg/m2 was found in 33%of the nonerosive reflux disease and in 18% of the erosive reflux disease patients(Carlsson *et al.*, 1998). A hiatal hernia was found more frequently in patients with erosive reflux disease (60%) than in those with nonerosive reflux disease (34%)(Smout, 1997).

Again, these findings are in accordance with the clinical impressions of many physicians of endoscopy-negative acid reflux disease.(Smout, 1997) An evaluation of a young Australian cohort demonstrated a positive association between an increased BMI and GERD symptoms. Then another large population-based questionnaire survey in Xi'an, China demonstrated a similar association ; however, another Chinese study showed no association between BMI and symptoms (Corley and Kubo, 2006) . The Japanese study reported a significant inverse association between BMI and GERD among males (Furukawa *et al.*, 1999). Rosaida *et al.*(Rosaida and Goh, 2004) also reported Indian and Malay ethnicity, and BMI ≥ 25 were significant independent risk factors for NERD.

1.5 Pathophysiology of NERD

Recent studies have provided greater insight into the pathophysiology and symptom generation in NERD. The major concepts in the pathophysiology include the pattern of mucosal response to gastric contents during reflux and on mucosal factors that may affect symptom perception(Chen and Hsu, 2013a).

Both esophageal dysmotility and hiatal hernia are less common in NERD than in erosive reflux disease (ERD)(Wu *et al.*, 2007). The pathophysiology as reduced ability to clear acid from the esophagus following reflux events in patients with ERD is thus uncommon in NERD patients; however, the latter group is characterized by greater esophageal sensitivity in the proximal esophagus (Emerenziani *et al.*, 2009).

Despite no difference in gastric acid output between NERD and ERD (Ho and Kang, 1999), NERD patients have lower acid reflux when compared with patients with erosive reflux disease (ERD) and Barrett's esophagus (Martinez *et al.*, 2003). In addition, there is considerable overlap in acid exposure times between three groups of GERD patients (Shapiro *et al.*, 2006). Proximal migration of acid and nonacidic reflux seems to play a role in the symptom generation in NERD (Emerenziani *et al.*, 2009).

Total acid and weakly acidic reflux are greater in erosive reflux disease (ERD) and Barrett's esophagus than in NERD (Bredenoord *et al.*, 2009), but NERD patients are shown to be of more homogenous distribution of acid exposure throughout the esophagus with greater proximal reflux (Dickman *et al.*, 2006).

With the advantage of impedance studies, NERD patients are shown to have greater proximal extent of reflux episodes (with and without prolonged esophageal acid exposure) than in healthy controls (Bredenoord *et al.*, 2006). Further studies have shown greater proximal extent of reflux events which appears to be associated with symptom perception in GERD patients refractory to acid-suppression therapy (Zerbib *et al.*, 2008).

Furthermore, some of the NERD patients are more sensitive to weakly acid reflux than those with erosive reflux disease (ERD) (Emerenziani *et al.*, 2008), supporting the explanation for poor PPI response in NERD patients. The potential explanations for the symptom generation in NERD include microscopic inflammation, visceral hypersensitivity (stress and sleep), and sustained esophageal contractions (Van Malenstein *et al.*, 2008)

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1.6 Clinical manifestation of NERD

. Currently, there are no specific clinical features that can differentiate NERD from erosive reflux disease (ERD) or even Barrett's oesophagus. There are also no clinical predictors for patients with functional heartburn. This means that these patients cannot be identified on a clinical basis only. Severity, frequency, or intensity of symptoms, have been shown to be similar, consistently, among the different reflux disease phenotypes(Simmonds, 2012). Furthermore, patients with different degrees of esophageal acid exposure have a similar symptom presentation.

The typical symptoms of GERD are recognized as heartburn and/or acid regurgitation. (Chen and Hsu, 2013b). Heartburn is commonly used to describe a burning sensation behind the sternum (breastbone), rising up toward the throat or the neck. It is important to remember that many patients use this term to describe many non esophageal causes, such as cardiac chest pain(Simmonds, 2011).

Regurgitation presents as a bitter or sour taste in the mouth. Regurgitation is less common than heartburn, and more difficult to control with anti-reflux treatment. It is exacerbated when bending over, or assuming the supine position(Simmonds, 2011).

NERD may also present with coughing, wheezing, a sore throat, chest pain, and other extraoesophageal manifestations. Furthermore, there are atypical signs that could be found, albeit rare, in NERD, which are similar to those found in ERD, such as hoarseness of voice (laryngeal involvement) and wheezing (pulmonary involvement)(Simmonds, 2011).

In addition, previous studies have shown that NERD patients appear to be less responsive to proton pump inhibitors (PPIs) as compared with patients with erosive esophagitis(Chen and Hsu, 2013b)

1.7 Upper gastroesophageal endoscopy

As stated in the definition, the diagnosis of NERD depends on the exclusion of erosive disease by upper endoscopy. Currently, NERD is differentiated from ERD by white light endoscopy, and NERD further differentiated from functional heartburn by using pH monitoring (± impedance) with symptom reflux association.

The diverse characteristics of NERD are apparent on endoscopy. Erosions are absent in these patients, but changes such as reddish or whitish discoloration are sometimes seen in areas of the esophageal mucosa. Others patients may display normal esophageal mucosa without such changes.

Some studies have employed a modified Los Angeles (LA) classification system, in which two grades, grade M (minimal changes such as erythema without sharp demarcation, whitish turbidity, and/or invisibility of vessels due to these findings), and grade N (esophagus without any such minimal changes or mucosal breaks) are added to the usual LA grades A, B, C, and D. Identifying minimal endoscopic changes can prove difficult for endoscopists with standard knowledge, and thus represents one obstacle for the utilization of minimal changes in classifications of GERD(Joh *et al.*, 2007).

The "L.A." (Los Angeles) classification describes four grades of esophagitis severity (A to D)(Lundell *et al.*, 1999), based on the extent of esophageal lesions known as "mucosal breaks" are used for ERD classification, but it does not record the presence or severity of other GERD lesions:

Grade A: One or more mucosal breaks each ≤5 mm in length

Grade B: At least one mucosal break >5 mm long, but not continuous between the tops of adjacent mucosal folds.

Grade C: At least one mucosal break that is continuous between the tops of adjacent mucosal folds, but which is not circumferential

Grade D: Mucosal break that involves at least three-fourths of the luminal circumference.

In general, the value of endoscopy in discovering GERD-related findings in patients with refractory GERD is very low. This is primarily due to the predominance of NERD and functional heartburn patients among this group of patients and the high efficacy of PPIs in healing erosive esophagitis. (Hershcovici and Fass, 2010a).

Besides that, for patients with eosinophilic esophagitis, the endoscopic abnormalities described mostly in this patients are not specific and can be present in gastroesophageal reflux disease (GERD) population(García-Compeán *et al.*, 2011).They have very diverse frequency mostly in studies with small number of patients: mucosal fragility or edema in 0–100%, concentric rings in 0–85%, strictures in 0–39%, whitish plaques and longitudinal furrows in 0–53% (Sgouros *et al.*, 2006).

These ample ranges may be partially explained to difficulties in recognizing some of these endoscopic abnormalities by non-expert endoscopists particularly in settings with low prevalence of EoE (García-Compeán *et al.*, 2011). In one of the few reports comparing endoscopic findings in patients with EoE to those with non-refractory GERD, concentric rings, strictures, lineal furrows and white plaques were significantly more frequent in the former patients (Dellon *et al.*, 2009).

Although all of these abnormalities were more frequent in patients with EoE , only rings and strictures reached statistically significant differences. Nevertheless none of them were predictive of EoE and can be present in GERD population(Dellon *et al.*, 2009).

1.8 Histological features of NERD

Biopsy has been utilized as potentially appealing investigations for the diagnosis of NERD. The role of mucosal biopsy to detect histopathological changes consistent with GERD remains an area of controversy in patients (off or on anti-reflux medication) who undergo upper endoscopy. Although commonly carried out in clinical practice if no visible abnormality is detected, they can be useful to exclude specific diagnoses, such as eosinophilic oesophagitis(Simmonds, 2011).

For establishing a histological diagnosis of gastroesophageal reflux disease (GERD) without Barret's mucosa, the literature gives following parameters(Vieth *et al.*, 2003):

- Basal zone hyperplasia(Ismail-Beigi *et al.*, 1970; ISMAIL and POPE II, 1974)
- Elongation of papillae(ISMAIL and POPE II, 1974).
- Infiltration of squamous epithelial with neutrophilic granulocytes with and without necrosis
- Eosinophilic granulocytes and lymphocytes(Leape *et al.*, 1981)
- Congestion and ectasia in capillary vessels ascending in epithelial papillae as well as thickened vessel walls
- Glycogen acantosis of squamous epithelium
- Spongiosis of squamous epithelium with dilated intracellular spaces
- Eosinophilic densification of the superficial cell layer

A recent study showed that the diagnostic role of histology in patients with GERD should be reconsidered as it has higher rates of sensitivity and specificity. Histology able to provide useful and objective additional data in 76% of patients with NERD. They suggest biopsies should be taken from Z-line and 2 cm above in order to optimize the diagnostic yield(Zentilin *et al.*, 2005).

To date, there has been little standardization of biopsy techniques, and no consensus on the number of biopsy specimens obtained, or the locations of the esophagus at which biopsies should be taken. From previous studies, biopsies have been obtained at the squamocolumnar junction (gastroesophageal junction), or at 1,2,3, and 5 cm above it .

Studies are still questioning the yield of esophageal mucosal biopsies as a diagnostic tool in NERD patients(Schindlbeck *et al.*, 1996; Simmonds, 2011). Its advantages are ease, convenience and low risk but no consensus exists regarding where to biopsy or how traditionally regarded histologic markers of reflux disease should be interpreted.

1.9 24-hours ambulatory pH-impedance monitoring

24-hours ambulatory pH-impedance monitoring is essential for diagnosing NERD, especially after the recent introduction of new definitions for functional heartburn by the Rome III Committee for Functional Esophageal disorders (Drossman, 2006).

24-hour esophageal pH monitoring has been criticized for having limited sensitivity in diagnosing GERD; however, this technique is still essential for the diagnosis of NERD. The limitation of conventional pH monitoring has been overcome by combining pH with impedance monitoring.

Impedance-pH monitoring is a novel technique that allows detection of all reflux events, distinguishing acid from non-acid (weakly acidic and weakly alkaline) refluxes. Reflux symptoms persisting despite acid suppressive therapy may be associated with either acid or non-acid reflux, or unrelated to reflux episodes.

Impedance-pH monitoring is currently emerging as the new gold standard for clarifying the mechanisms of proton pump inhibitor(PPI)-refractory symptoms(Bredenoord, 2008). It is also considered the best method to relate refractory symptoms to reflux but whether it should be performed on or off PPI therapy is still debated(Bredenoord, 2008; Hemmink *et al.*, 2008; Kahrilas and Smout, 2010).

By impedance–pH monitoring, patients with endoscopy-negative refractory heartburn can be subdivided into NERD or functional heartburn (FH), the former defined as the presence of typical symptoms of GERD caused by reflux, in the absence of mucosal injury at endoscopy(Hershcovici and Fass, 2010b), and the latter defined as absence of evidence that reflux is the cause of the symptoms(Kahrilas and Smout, 2010).

Among 33-50% of NERD patients will demonstrate normal acid exposure over 24 hours. However, there is evidence that abnormalities exist at the microscopic level in NERD patients, including dilated intercellular spaces on electron microscopy. (Fass, 2007)

Esophageal pH monitoring is commonly used in the evaluation of patients with refractory GERD. In the assessment of such patients, pH monitoring can be performed off PPI to test if the initial diagnosis was correct (i.e., heartburn was due to acid reflux) or on PPI to test whether the symptoms are due to residual acid reflux.

Inclusion of a symptom–reflux correlation measure such as symptom index (SI) and/or symptom association probability (SAP) helps to determine the relationship between heartburn episodes and acid reflux events, regardless if the pH test is normal or abnormal. (Hershcovici and Fass, 2010a)

2.OBJECTIVES AND HYPOTHESIS

2.1 Study objectives

2.1.2 General objective

This study is aim to determine the mean severity score of symptoms, endoscopic features, histology and pH-metric in NERD (non erosive reflux disease) in all patients undergoing OGDS in Hospital Universiti Sains Malaysia Kubang Kerian , Kelantan .

2.1.2 Specific objectives

1. To determine association of mean of symptom severity with endoscopic features in non-erosive reflux disease (NERD).
2. To determine the association of endoscopic features with pH findings in non-erosive reflux disease (NERD).
3. To determine the prevalence of eosinophilic esophagitis in nonerosive reflux disease(NERD) population.

2.2 Study hypothesis

2.2.1 Study questions

1. Are there interactions and associations between the symptoms severity and the endoscopic changes in the NERD population?

2. Are there any association between any endoscopic features and the 24-hours ambulatory pH-impedance study in NERD population?

3. Are there any cases of eosinophilic esophagitis in the NERD population?

2.2.2 Study hypothesis

1. Alternative: There is an association between symptoms severity and endoscopic changes in NERD population.

Null: There is no association between symptoms sweating and endoscopic changes in the NERD population

2. Alternative: There is an association between the endoscopic feature and positive 24-hours ambulatory pH-impedance study in NERD population.

Null: There is no association between the endoscopic feature and positive 24-hours ambulatory pH-impedance study in NERD population.

4. Alternative: There is presence of eosinophilic esophagitis in NERD population.

Null: There is no eosinophilic esophagitis in NERD population.

3.METHODOLOGY

3.1 Study design

This was a prospective study.

3.2 Study approval

This study was approved by the Research and Ethic Committee, Universiti Sains Malaysia on 10 January 2012.

Reference number : FWA Reg No 00007718 IRB Reg. No: 00004494 (Appendix 1)

3.3 Study population and study sampling

This study was conducted between June 2014 until November 2014 in Hospital Universiti Sains Malaysia Kubang Kerian, Kelantan. All patient presented either to Gastrointestinal Clinic or Endoscopy unit complaining of any gastrointestinal symptoms such as dysphagia, abdominal pain, heartburn, reflux symptoms, nausea, vomiting, nocturnal cough or odynophagia and were indicated for OGDS was selected based on inclusion and exclusion criteria.

All the patients that fulfill the inclusion and exclusion criteria would be explained regarding the study topic and procedures conducted, and consent obtained once patient agreed to involve in the study (Appendix 2). Then a simple interview and details regarding demographic data, medical history and symptoms were obtained using a questionnaire (Appendix 3).

The patient involved would be prepared by the staff nurse in charge of the endoscopic room, and endoscopic procedure performed by the Gastroenterologist (Lee YY). Endoscopic features will be reviewed and photographs taken for each level respectively and details will be recorded in the OGDS data collection form (Appendix 4).

All patient who had normal endoscopic findings (NERD) were consented for 24-hour ambulatory pH-impedance monitoring.

3.4 CHARACTERISTIC OF SUBJECTS

3.4.1 Inclusion criteria**:**

Patients:

1. Age 18 years and above.
2. Having symptoms of :
    - Dysphagia
    - Abdominal pain
    - Heartburn
    - Non-cardiac chest pain
    - Nausea
    - Vomiting
    - Refractory reflux
    - Odynophagia
    - Hoarseness of voice
    - Nocturnal cough
    - Bloatedness