

A comparative study on effects of three measuring methods for gastroesophageal reflux of post-POEM achalasia patients

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Abstract

Background: Gastroesophageal reflux is a major complication of post-POEM (peroral endoscopic myotomy, POEM) for esophageal achalasia. **Objective:** To discuss the effects of three measuring methods for Gastroesophageal Reflux of Post-POEM Achalasia Patients and find out the best method for diagnosing post-POEM gastroesophageal reflux of esophageal achalasia patients by conducting clinical follow-up studies. **Methods:** Follow-up visits were conducted on the patients with esophageal achalasia who had received POEM treatment in our hospital from 2013 to 2016. Between 2 to 4 weeks post operation, Eckardt score was adopted to evaluate the operation efficacy, the GerdQ score, electronic gastroscopy and 24h esophagus impedance-pH monitoring to investigate the gastroesophageal reflux and the comparison of detection rate among the three different methods on post-POEM gastroesophageal reflux. **Results:** There were 76 patients with Eckardt scores were 3 or lower than 3 post POEM (76/78, 97.44%), 2 patients with Eckardt scores were 4 or higher than 4 (2/78, 2.56%), the cure rate of the treatment was as high as 97.44%; the Eckardt score post operation decreased more significantly than before operation, $P < 0.05$. **Conclusion:** for post-POEM Achalasia patients, 24h esophagus impedance-pH monitoring is the best way to diagnose post-POEM gastroesophageal reflux.

Keywords: Esophageal Achalasia; Gastroesophageal reflux; peroral endoscopic myotomy; 24h esophagus impedance-pH monitoring.

Practical Application: Best method for diagnosing post-POEM gastroesophageal reflux using 24h esophagus impedance-pH monitoring.

1 Introduction

Gastroesophageal reflux is a major complication of post-POEM (peroral endoscopic myotomy, POEM) for esophageal achalasia, and long-lasting gastroesophageal reflux may cause esophageal stenosis and Barrett esophagus canceration, which affects the long-term treatment effects of POEM. The occurrence rates reported in the literature show large differences which may be caused by different methods. Therefore, it is necessary to find out the most effective and the most objective way to diagnose post-POEM gastroesophageal reflux.

The cause of esophageal achalasia is not known yet, and the major features of this disease include reduction of esophageal peristalsis, increasing pressures of lower esophageal sphincters, and worse relaxation response of lower esophagus and cardia when swallowing, which leads to food blockade. The clinical symptoms of this disease include intermittent dysphagia, emesis, retrosternal pain or discomforts. Since the cause of esophageal achalasia is not known yet, it has been difficult to cure this disease clinically; currently, the treatments on this disease have relieved the clinical symptoms.

In 2008, the POEM (peroral endoscopic myotomy, POEM) was firstly applied to the treatment of esophageal achalasia, which was first reported by the Japanese scholar Inoue. Being a major method to treat achalasia, it is widely accepted to be with good

short-term therapeutic effects and high security. Long-term complications include gastroesophageal reflux, which might lead to esophageal stenosis and thus affect the long-term therapeutic effects of POEM; therefore, detecting post-POEM gastroesophageal reflux and timely intervention are of great importance in terms of clinical studies. By conducting symptomatic scoring (GerdQ scores), electronic gastroscopy and 24h esophagus impedance-pH monitoring, the authors try to investigate the situations of post-POEM gastroesophageal reflux and aim to find out the best method of diagnosing post-POEM gastroesophageal reflux.

2 Material and methods

2.1 Study subjects

Seventy Eight esophageal achalasia patients with the average age of 36.68 ± 10.89 , who received POEM in our hospital during 2013 to 2016, including 31 males (31/78, 39.74%) and 47 females (47/78, 60.26%) were studied.

2.2 Study methods

2.1 Post-POEM Eckardt Scoring: the Eckardt Scoring systems include weight loss, dysphagia, retrosternal pain

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and reflux, each index was categorized into four degrees, i.e.: none, occasionally, every day, and every meal with 0-3 points respectively. (See Table 1)

2.2.1 Effect evaluation of post-POEM Esophageal Achalasia

The effect evaluation was usually conducted between 2 to 4 weeks post POEM, Eckardt Scoring was conducted on the patients' post-operative symptoms. The Eckardt Scores were lower than or equal to 3, the treatment was thus considered to be effective. Within 6 months post operation, if the Eckardt Scores were equal to 4 or were higher than 4, then the treatment was considered to be failure (Eckardt & Eckardt, 2011; Eckardt et al., 1992).

2.2.2 GerdQ Scoring

The patients were asked to recall the frequency of heartburn and reflux (S+, positive symptoms), or the frequency of upper abdominal pain and nausea (S-, negative symptoms), and the frequency of being unlikely to sleep well at night due to heartburn or reflux, as well as extra taking of medicines to ease heartburn and/or reflux (I+, Positive Influence), these three indexes were categorized into four degrees, namely 0 day, 1 day, 2-3 days and 4-7 days and they were evaluated by 0-3 points respectively, those who got three indexes ≥ 8 were considered to be gastroesophageal reflux.

2.2.3 Electronic gastroscopy examination

Reexaminations of electronic gastroscopy were conducted one month post the POEM to detect whether there was reflux esophagitis. The reflux esophagitis were diagnosed according 1994 Los Angeles Grading Standard, and according to which, the reflux esophagitis could be graded from A to D.

2.2.4 The 24h esophagus impedance-pH monitoring: (Sifrim et al., 2004) DeMeester integration

The integration systems included the percentage of Ph<4 was in the whole period, the time percentage of Ph<4 was in upright position, the time percentage of Ph<4 was in lying position, the total times of acid reflux, the times of acid reflux were >5 minutes, the maximum duration of reflux, DeMeester integration were ≥ 15 points detecting positive, which indicated pathological acid reflux. (Zerbib et al., 2005) Categories of reflux: acid reflux: Ph<4, weak acid reflux: $4 \leq \text{Ph} \leq 7$ and alkali reflux: Ph>7, the latter two were called non-acid reflux (Inoue et al., 2010).

Table 1. Clinical Symptomatic Scoring Systems of Achalasia.

Scores	Symptoms			
	Weight Loss(Kg)	Dysphagia	Retrosternal Pain	Reflux
0	None	None	None	None
1	<5	Occasionally	Occasionally	Occasionally
2	5-10	Everyday	Everyday	Everyday
3	>10	Every Meal	Every Meal	Every Meal

Kg: kilogram

According to the features of Impedance-PH Monitoring system and the Impedance-PH results in the literature, when the median of acid reflux events was ≥ 35 , median of weak acid reflux events was ≥ 18 , and median of alkali reflux events was ≥ 7 , the result that met any one of the above standard was considered to be positive of Impedance-PH Monitoring (Sharma et al., 2006).

2.3 Statistical analysis

The program SPSS 15.0 was adopted to analyze the data, the measurement data was MEAM \pm STANDARD DEVIATION ($\bar{x} \pm s$), the Eckardt Scoring was measured by *t* test and the comparison of rates between groups was measured by χ^2 test, when $p < 0.05$, the differences had statistical significance.

3. Results

3.1 Evaluation of post-POEM effects.

There were 76 patients with Eckardt scores were 3 or lower than 3 post POEM (76/78, 97.44%), 2 patients with Eckardt scores were 4 or higher than 4 (2/78, 2.56%), the cure rate of the treatment was as high as 97.44%; the Eckardt score post operation decreased more significantly than before operation, $P < 0.05$; therefore, the point differences between the two groups had statistical significance. (See Table 2)

3.2 Occurrence of post-POEM gastroesophageal reflux

3.2.1 Results of GerdQ Scoring

62 patients received GerdQ Scoring post POEM, and results showed that 8 of them experienced gastroesophageal reflux (8/ 62, 12.90%).

3.2.2 Results of electronic gastroscopy

56 patients returned to the hospital and received examinations of electronic gastroscopy, and the results showed that 6 suffered from reflux esophagitis (6/56, 10.71%), including 4 Grade A reflux esophagitis (4/56, 7.14%) and 2 Grade B reflux esophagitis (2/56, 3.57%).

3.2.3 Twenty-four hours esophagus impedance-pH monitoring

32 patients received the 24h esophagus impedance-pH monitoring, 6 patients of them suffered from esophageal pathologic acid reflux (6/32, 18.75%), 12 patients with non-acid reflux (12/32, 37.5%) and 1 patient with mixed reflux (1/32, 3.13%), the general detection rate of gastroesophageal reflux was as high as 59.38%; 8 of the 32 patients were detected by GerdQ and 6 of them were detected by electronic gastroscopy.

Table 2. Comparison of Eckardt scoring before and after POEM.

	Before POEM	After POEM
Eckardt scoring	7.05 \pm 1.14	1.33 \pm 1.16*

* vs POEM before the operation, $P < 0.05$. POEM: peroral endoscopic myotomy

3.2.4 The comparison of the detection rates of the three methods on gastroesophageal reflux

The difference of detection rate between GerdQ and electronic gastroscopy had no statistical significance, $P > 0.05$, whereas the detection rate of 24h esophagus impedance-pH monitoring was higher than that of the other two methods, $P < 0.05$, and the difference had statistical significance. (See Table 3)

4. Discussion

Esophageal achalasia is a rare disease with an occurrence rate of 1/100000 per year, which is higher in Europe and North America than in other regions, and there is no obvious difference between genders in terms of occurrence rate, the likely occurrence rate ages are from 30 to 40. In 2008, POEM was firstly applied to the treatment of esophageal achalasia, due to its sound short-term effects and high security (Von Renteln et al., 2013), it has been widely accepted and adopted around the world, and the long-term complication of POEM is gastroesophageal reflux.

In the mechanism of gastroesophageal reflux, the destruction of anti-reflux barriers is the major cause, the anti-reflux barriers of esophagus include LES (lower esophageal sphincter, LES), crura of diaphragm, phrenicoesophageal ligament, angle and magenblase, etc. and the functions of LES among them are the most important. POEM needs to cut off the LES circular muscle and even part of the longitudinal esophageal muscles, which leads to deterioration of the functions of the anti-reflux barriers, thus it is believed that POEM causes increase of occurrence rate of gastroesophageal reflux. The long-term existing gastroesophageal reflux might lead to complications of Barrett esophagus and esophageal stenosis, and the chronic esophageal ulcer and inflammation may cause cicatrix and esophageal stenosis, it is often spotted on lower esophagus clinically, esophageal stenosis might cause dysphagia and thus be contrary to the original intentions of POEM, among the Barrett esophagus patients who were not detected atypical hyperplasia during the first gastroscopy, half of them will develop to high grade intraepithelial neoplasia or early esophageal cancer (Linghu et al., 2014), The canceration of Barrett esophagus might lead to the fact that the long-term risks of POEM are higher than its long-term benefits. Since the occurrence rates of short-term complications of POEM are low, such as bleeding, perforation and infections, the treatment effects will not be badly influenced, so compared with the short-term

complications of POEM, such as bleeding, perforation and infections, post-POEM gastroesophageal reflux has a greater clinical significance on the treatment effect of POEM, especially in long-term. Therefore, it is necessary to further study on the situations of post-POEM gastroesophageal reflux and to find out the best method to diagnose post-POEM gastroesophageal reflux, so as to discover and appropriately handle post-POEM gastroesophageal reflux to ensure the long-term effects of POEM.

The literatures both at home and abroad show that the occurrence rate of post-POEM gastroesophageal reflux varies from 5.88% to 60% (Von Renteln et al., 2013; Linghu et al., 2014; Hungness et al., 2013; Verlaan et al., 2013; Inoue et al., 2010; Swanstrom et al., 2012), and the evaluation methods include symptomatology evaluation, endoscopic diagnosis and 24h Ph monitoring of esophagus. In 2010, Inoue H (Hungness et al., 2013) reported 17 post-POEM patients who received electronic gastroscopy examination and 1 of them suffered from gastroesophageal reflux (Grade B of Los Angeles Standard), the occurrence rate of gastroesophageal reflux was 5.88%, in 2012, Swanstorm (Verlaan et al., 2013) conducted follow-up observations on 18 esophageal achalasia patients, 6 months after the operation they received 24h esophagus Ph monitoring and the occurrence rate of gastroesophageal reflux was 46%; in 2013, Verlaan (Inoue et al., 2010) reported 6 cases of reflux esophagitis under the electronic gastroscopy among 10 post-POEM patients, the occurrence rate of gastroesophageal reflux was 60%; in 2014 Linghu Enqiang (Swanstrom et al., 2012) analyzed the occurrence of gastroesophageal reflux of 41 post-POEM patients and the occurrence rates of gastroesophageal reflux three months post operation with symptomatic evaluation and electronic gastroscopy were respectively 26.83% and 27.27%; in 2014, Teitelbaum EN (Teitelbaum et al., 2014) conducted a follow-up visit on 41 patients for more than 1 year post POEM, according to the GerdQ scores, the occurrence rate of gastroesophageal reflux was 15%, 13 patients of all the follow-up patients received 24h Ph monitoring of esophagus, and 4 of them (31%) experienced esophageal pathologic acid reflux. Due to the simple operations, good compliance of patients and maturity of technology of symptomatology evaluation and endoscopic diagnosis, the two methods are the most commonly seen methods clinically, whereas the operation of 24h Ph monitoring of esophagus is more complicated, the technology is not so popularized, operation invasiveness, long duration of operation, low compliance of patients and low repetitiveness, there are limitations on such methods to be used clinically. So far, there has been no report in the literature on the 24h esophagus impedance-pH monitoring post POEM.

There were limitations for symptomatology evaluation and endoscopic diagnosis, the former was greatly influenced by subjective elements, and the latter cannot spot negative-endoscopy reflux diseases, which might lead to misdiagnose or missed diagnose, so the efficacy is low, and the pure 24h esophagus Ph Monitoring can only spot pathological acid reflux but cannot spot non-acid reflux, so there might be some missed diagnose, thus it cannot be regarded as the golden standard of diagnosing gastroesophageal reflux. Dalby (Dalby et al., 2007) found out that the detection rates of non-acid reflux in reflux esophagitis and negative-endoscopy reflux diseases were 20% and 38%

Table 3. Comparisons of Detection Rate of Three Methods on post-POEM Gastroesophageal Reflux.

	Total (person)	Gastroesophageal Reflux(person)	Detection Rate(%)
GerdQ Scoring	62	8	12.90 [▲]
Electronic Gastroscopy	56	6	10.71 [*]
24h esophagus impedance-pH monitoring	32	19	59.38

^{*} vs 24h esophagus impedance-pH monitoring, $P < 0.05$; [▲] vs Electronic Gastroscopy, $P > 0.05$ POEM: peroral endoscopic myotomy

by impedance Ph study, whereas the pure 24h esophagus Ph monitoring could not detect these kind of reflux. 24h esophagus impedance-pH monitoring was affected by subjective elements and it could spot those negative-endoscopy reflux diseases and those non-acid reflux that pure 24h esophagus-pH monitoring cannot detect; therefore, it is the best way with the highest detection rate so far. The present study showed that by GerdQ scoring and electronic endoscopy, the detection rates of gastroesophageal reflux were 12.90% and 10.71% respectively, the inter-group difference had no statistical significance, whereas the detection rate by 24h esophagus impedance-pH monitoring was as high as 59.38%, which was much higher than the that of the former two methods and the difference had statistical significance, which also proved that the efficacy of 24h esophagus impedance-pH monitoring was much higher than other methods, therefore, it is highly recommended that 24h esophagus impedance-pH monitoring can be adopted to improve the detection rate of gastroesophageal reflux after POEM.

Besides all the acid reflux and non-acid reflux, the 24h esophagus impedance-pH monitoring could also detect the nature and height of the reflux contents and the relevance between the reflux and symptoms; therefore, it provided references for the alternatives of treating gastroesophageal reflux diseases, the determination of treatment efficacy and the causes of refractory gastroesophageal reflux diseases. Emerenziani et al. (2008) studied on negative-endoscopy reflux diseases patients with esophagus impedance-pH detection and found out when the acid exposure was normal, 2/3 of the patients' symptoms would be relevant with mixed reflux of gas and liquid, and noted that the gas might improve the perpetual abilities of esophagus on the contents inside, which led to the fact that weak acid reflux may also cause clinical symptoms, but due to the minor injury of weak acid reflux on the esophageal mucosa, esophagitis couldn't be spotted under the endoscopy. Dai et al. (2013) conducted a measuring study of 24h esophagus impedance-pH monitoring on patients with non-erosive reflux, and the results showed that proximal reflux of the esophagus of the non-erosive reflux patients took place more frequently than those of the control group, and noted that proximal reflux of the esophagus is the major cause of non-erosive reflux. Bredenoord et al. (2005) found that when the duration of acid exposure was normal by 24h esophagus impedance-pH monitoring, 36% of the gastroesophageal reflux disease patients might experience proximal reflux of the esophagus, which was 19.5% higher than the normal control group, and the results further supported the fact that proximal reflux of the esophagus was the main cause of reflux symptom. Mainie et al. (2006) conducted follow-up visits on patients who received laparoscopic fundoplication and found that when the reflux symptoms were relevant with weak acid reflux, good treatment effects of anti-reflux operation could be achieved, whereas if the reflux symptoms were not relevant with the weak acid reflux, the anti-reflux operation might not get a good result. Thus it can be seen that the 24h esophagus impedance-pH monitoring can analyze in details the features of gastroesophageal reflux, more importantly, it can be used by clinical doctors to guide clinical treatment. Non-acid reflux might be relevant with bile or duodenal juice, therefore, in terms of the alternatives of medicines, besides using proton pump inhibitor

to restrain gastric acid, hydrotalcite and ursodesoxycholic acid can also be used to neutralize bile, which might achieve better treatment effects. If obvious clinical symptoms were caused by the over height of reflux, the doctors can instruct the patients to avoid increasing abdominal pressure and avoid eating too much or lying down right after meals. Besides, 24h esophagus impedance-pH monitoring can be applied to the evaluations of anti-reflux treatment, Bredenoord conducted study on the treatment effects of anti-reflux operations by 24h esophagus impedance-pH monitoring and found that the anti-reflux treatments can reduce the frequency of all types of reflux and noted that this method can achieve sound treatment effects. Therefore, for post-POEM Achalasia patients, 24h esophagus impedance-pH monitoring is the best way to diagnose post-POEM gastroesophageal reflux.

References

- Bredenoord, A. J., Weusten, B. L., Timmer, R., & Smout, A. J. (2005). Reproducibility of multi-channel intraluminal electrical impedance monitoring of gastroesophageal reflux. *The American Journal of Gastroenterology*, 100(2), 265-269. <http://dx.doi.org/10.1111/j.1572-0241.2005.41084.x>. PMID:15667480.
- Dai, F., Chen, F., Qiu, S., Wang, X., & Zhang, J. (2013). The value of 24-hour multichannel intraluminal esophageal impedance-pH monitoring in differentiating NERD and functional heartburn patients. *Chinese Journal of Clinicians*, 7(14), 6379-6382.
- Dalby, K., Markow, S., Pontø, C. H., & Kruse-Andersen, S. (2007). Multiple intraluminal impedance measurement in the esophagus. Experience with the first 100 Danish patients. *Ugeskrift for Laeger*, 169(42), 3579-3583. PMID:18031670.
- Eckardt, A. J., & Eckardt, V. F. (2011). Treatment and surveillance strategies in achalasia: an update. *Nature Reviews. Gastroenterology & Hepatology*, 8(6), 311-319. <http://dx.doi.org/10.1038/nrgastro.2011.68>. PMID:21522116.
- Eckardt, V. F., Aignherr, C., & Bernhard, G. (1992). Predictors of outcome in patients with achalasia treated by pneumatic dilation. *Gastroenterology*, 103(6), 1732-1738. [http://dx.doi.org/10.1016/0016-5085\(92\)91428-7](http://dx.doi.org/10.1016/0016-5085(92)91428-7). PMID:1451966.
- Emerenziani, S., Sifrim, D., Habib, F. I., Ribolsi, M., Guarino, M. P., Rizzi, M., Caviglia, R., Petitti, T., & Cicala, M. (2008). Presence of gas in the refluxate enhances reflux perception in non-erosive patients with physiological acid exposure of the oesophagus. *Gut*, 57(4), 443-447. <http://dx.doi.org/10.1136/gut.2007.130104>. PMID:17766596.
- Hungness, E. S., Teitelbaum, E. N., Santos, B. F., Arafat, F. O., Pandolfino, J. E., Kahrilas, P. J., & Soper, N. J. (2013). Comparison of perioperative outcomes between peroral esophageal myotomy(POEM) and laparoscopic Heller myotomy. *Journal of Gastrointestinal Surgery: Official Journal of the Society for Surgery of the Alimentary Tract*, 17(2), 228-235. <http://dx.doi.org/10.1007/s11605-012-2030-3>. PMID:23054897.
- Inoue, H., Minami, H., Kobayashi, Y., Sato, Y., Kaga, M., Suzuki, M., Satodate, H., Odaka, N., Itoh, H., & Kudo, S. (2010). Peroral endoscopic myotomy (POEM) for esophageal achalasia. *Endoscopy*, 42(4), 265-271. <http://dx.doi.org/10.1055/s-0029-1244080>. PMID:20354937.
- Linghu, E., Wang, N., Wang, X., Du, H., Meng, Y., Wang, H., & Zhu, J. (2014). Clinical curative effect of asymptotic full-thickness myotomy type of peroral endoscopic myotomy on 41 cases of achalasia. *Chinese Journal of Digestive Endoscopy*, 2014(8), 435-438.

- Mainie, I., Tutuian, R., Shay, S., Vela, M., Zhang, X., Sifrim, D., & Castell, D. O. (2006). Acid and non-acid reflux in patients with persistent symptoms despite acid suppressive therapy: a multicentre study using combined ambulatory impedance-pH monitoring. *Gut*, 55(10), 1398-1402. <http://dx.doi.org/10.1136/gut.2005.087668>. PMID:16556669.
- Sifrim, D., Castell, D., Dent, J., & Kahrilas, P. J. (2004). Gastroesophageal reflux monitoring: review and consensus report on detection and definitions of acid non-acid and gas reflux. *Gut*, 53(7), 1024-1031. <http://dx.doi.org/10.1136/gut.2003.033290>. PMID:15194656.
- Sharma, P., Falk, G. W., Weston, A. P., Reker, D., Johnston, M., & Sampliner, R. E. (2006). Dysplasia and cancer in a large multicenter cohort of patients with Barrett's esophagus. *Clinical Gastroenterology and Hepatology*, 4(5), 566-572. <http://dx.doi.org/10.1016/j.cgh.2006.03.001>. PMID:16630761.
- Swanstrom, L. L., Kurian, A., Dunst, C. M., Sharata, A., Bhayani, N., & Rieder, E. (2012). Long-Term Outcomes of an Endoscopic Myotomy for Achalasia: the POEM Procedure. *Annals of Surgery*, 256(4), 659-667. <http://dx.doi.org/10.1097/SLA.0b013e31826b5212>. PMID:22982946.
- Teitelbaum, E. N., Soper, N. J., Santos, B. F., Arafat, F. O., Pandolfino, J. E., Kahrilas, P. J., Hirano, I., & Hungness, E. S. (2014). Symptomatic and physiologic outcomes one year after peroral esophageal myotomy(POEM) for treatment of achalasia. *Surgical Endoscopy*, 28(12), 3359-3365. <http://dx.doi.org/10.1007/s00464-014-3628-1>. PMID:24939164.
- Von Renteln, D., Fuchs, K. H., Fockens, P., Bauerfeind, P., Vassiliou, M. C., Werner, Y. B., Fried, G., Breithaupt, W., Heinrich, H., Bredenoord, A. J., Kersten, J. F., Verlaan, T., Trevisonno, M., & Rösch, T. (2013). Peroral endoscopic myotomy for the treatment of achalasia: an international prospective multicenter study. *Gastroenterology*, 145(2), 309-311. <http://dx.doi.org/10.1053/j.gastro.2013.04.057>. PMID:23665071.
- Verlaan, T., Rohof, W. O., Bredenoord, A. J., Eberl, S., Rösch, T., & Fockens, P. (2013). Effect of peroral endoscopic myotomy on esophagogastric junction physiology in patients with achalasia. *Gastrointestinal Endoscopy*, 78(1), 39-44. <http://dx.doi.org/10.1016/j.gie.2013.01.006>. PMID:23453184.
- Zerbib, F., des Varannes, S. B., Roman, S., Pouderoux, P., Artigue, F., Chaput, U., Mion, F., Caillol, F., Verin, E., Bommelaer, G., Ducrotté, P., Galmiche, J. P., & Sifrim, D. (2005). Normal values and day-to-day variability of 24-h ambulatory oesophageal impedance-pH monitoring in a Belgian-French cohort of healthy subject. *Alimentary Pharmacology & Therapeutics*, 22(10), 1011-1021. <http://dx.doi.org/10.1111/j.1365-2036.2005.02677.x>. PMID:16268977.