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Controversies of Gastro-Oesophageal Junction and "Gastric Cardia" and the role of Gastro-oesophageal reflux in it.

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INTRODUCTION

Gastro-oesophageal junction (GOJ) and the neighboring "gastric cardia" are two of the most enigmatic regions in the human body and has been the focus of controversy over many decades.

The significance of having a proper understanding about these regions is, adenocarcinoma in the lower oesophagus, GOJ and cardia are rising and in the West and this rise has gained dramatic proportions while in the South Asian region we are experiencing the early stages of increase (1 -4). In the USA, the relative incidence of esophageal adenocarcinoma (per squamous cell carcinoma) has risen from 23.9% to 161% during the 1976 – 2007 period (SEER cancer statistics), whereas in Sri Lanka, the rise is 4.8% to 14.3%, during 1999 to 2013 at Teaching Hospital, Peradeniya (4). According to Sri Lanka National cancer control programme data the relative incidence of oesophageal adenocarcinoma in 2019 is 19.3%.

The premalignant lesion for distal oesophageal adenocarcinoma is intestinal metaplasia (IM) i.e. Barrett Oesopahgus, as defined by American Gastroenterology guidelines and is associated with Gastro-oesophageal reflux disease (GORD) (5). The malignancy risk of IM of oesophagus is significantly higher than IM of the stomach (especially when it occurs without background gastric atrophy), hence the former requiring closer follow up (5,6). Furthermore, Oesophageal adenocarcinoma and gastric adenocarcinoma are also prognostically different and have different management protocols (7,8). Hence, correct identification of the GOJ, anatomically and histologically is important to correct classification of adenocarcinoma arising in this region and correct management of Barrett oesophagus.

Why is it difficult to correctly identify the GOJ?

Very high prevalence of gastro-oesophageal reflux (GOR) associated damage in the GOJ obliterate the anatomical landmarks of the junction. Since, most people have variable degree of GOR, symptomatic or asymptomatic, reflux related changes are very common making it difficult to differentiate normal from abnormal. The main abnormality causing GOR is dysfunction of the lower oesophageal sphincter (LOS), reduced or loss of tone of which, unable to prevent gastric content refluxing back into the oesophagus when the gastric pressure increases.

The commonly used endoscopic landmarks of the GOJ are, the end of tubular oesophagus, the Z line and the proximal limits of the gastric rugal folds. In

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a person with a normal GOJ, these three landmarks would correctly identify the junction. However, damaged LOS and reflux related glandular metaplasia of the distal oesophagus alter these landmarks, as discussed in detail subsequently. Since the changes are extremely common universally, especially in the West, where most of the studies have been carried out, there is no clear understanding of what is normal in this region.

In this oration, I would look at how the knowledge on the GOJ has evolved, the deficiencies in the current knowledge and my humble contributions to address these deficiencies. Furthermore, I would compare my experience with the Sri Lankan population with my research findings in a high GORD prevalent USA population.

History of the problem

From early 1900's there are surgical descriptions of presence of columnar mucosa in the distal oesophagus. In 1950, Norman Barrett, a renowned British surgeon, defined the oesophagus as the part which lined by squamous epithelium and hence, the GOJ is the junction between the squamous epithelium and gastric glandular mucosa. He described the columnar lined distal part of the oesophagus as tubular stomach which had got pulled up due to congenitally shortened oesophagus (9). However, in 1953, Allison and Johnstone identified that what Barrett described as tubular stomach did not have a peritoneal lining and the gastric type musculature and contained oesophageal type submucosal glands (10). Hence, they identified Barrett's tubular stomach as part of the oesophagus lined by gastric type mucosa (10). In 1957 Barrett acknowledged that Allison and Johnstone were correct and agreed to the term "columnar lined lower oesophagus" (11). Barrett, Allison and Johnstone still believed that the columnar lining in the oesophagus was congenital. However, later Barrett described the association of the Columnar lined lower oesophagus with what we now identify as gastro-oesophageal reflux as follows "if the cardiac valve of a normal person were to become incompetent and if the lower esophagus were, as a result, to be bathed for a long time by digestive gastric juice, the squamous epithelium could be eaten away and totally replaced by columnar cells (11). Later, studies done by Moersch *et. al.* in 1954 suggested and Bremner *et. al.* in 1970 confirmed that the columnar lined oesophagus (CLO) is metaplastic and due to gastro-oesophageal reflux (12,13).

To complicate matters further, in 1961, Hayward described that the normal GOJ is lined by a non-specialized mucin secreting columnar epithelium and he named this as junctional mucosa; he further stated that it was normal to have the lower 1 -2 cm of the esophagus lined by glandular mucosa (14). As a result, until early 1990's presence of a columnar lined oesophagus (CLO) up to 2cm in the GOJ was regarded as normal and a minimal length of 3cm above the gastro-oesophageal junction was required to make a diagnosis of CLO until the concept of short segment Barrett was put forward based on work by Spechler et.al. in 1994 (15). However, the 3cm rule and the use of the term junctional mucosa to describe the glandular mucosa found in the lower oesophagus and GOJ are still practiced by some surgeons and pathologists. Furthermore, our advanced level biology curriculum still teaches that the normal lower oesophagus is lined by glandular epithelium. Now it is widely accepted that the normal oesophagus is entirely lined by squamous epithelium. A normal GOJ is endoscopically identified as the end of the tubular oesophagus and on the mucosal side marked by the Z line and proximal limits of "gastric" rugal folds; the peritoneal reflection marks the GOJ on the serosal side (5.18). However, a completely normal GOJ is not a common finding. In GORD, the LOS is damaged resulting in reduced or loss of sphincter tone that alters the normal anatomy of the GOJ as described below; furthermore, due to columnar metaplasia the normal histology is changed. Because of the extremely high prevalence of GOR, in most, the GOJ is damaged to variable extent, blurring the normal histological and anatomical/endoscopic landmarks.

In the CLO, what we now know as metaplastic, there can be mainly three types of metaplastic glandular epithelia: Cardicac mucosa (CM), Oxyntocardiac Mucosa (OCM) and intestinal metaplasia (IM). The significance of these epithelial types was not evident until Haggit *et.al.* proposed that intestinal type metaplasia in the CLO significantly increases the risk of development of adenocarcinoma which later confirmed and re

confirmed by many others (13 – 17). Hence, IM of the lower oesophagus (identified as Barrett Oesophagus) is considered as the pre-malignant lesion of oesophageal adenocarcinoma.

Due to high prevalence of CM ± OCM in the GOJ region, it was widely believed that this is a normal part of the proximal most stomach and recognizes it "gastric cardia". It is also known that these epithelia could also be metaplastic as a result of GOR. Hence, the distal end of the oesophagus in people with reflux damage cannot be reliably defined. Furthermore, the cardia has been defined in various manners in textbooks and dictionaries and studies on its origin have shown variable results indicating the poor understanding of anatomy and histology of this region (18). The clinical significance of this is, presence of IM in the oesophageal mucosa carries a significantly higher risk of adenocarcinoma compared to IM in the proximal stomach (5,6,19). As a result, the aetiopathogenesis of the GOJ adenocarcinoma and cardia adenocarcinoma are highly debated. Furthermore, adenocarcinoma of the lower oesophagus, GOJ and cardia show a rising pattern, whereas, the distal gastric adenocarcinoma incidence is declining (20,21), indicating the aetiology of GOJ and Cardia adenocarcinoma is different from the rest of the stomach. Hence, presently, in persons with GOR related changes, we still do not know the correct location of the GOJ and whether the "cardia" is gastric or oesophageal.

Evidence to minimize the controversy

In two studies we carried out in University of Southern California (USC) which is a referral centre for GORD and Teaching Hospital Peradeniya (THP), we found that in the USC population those with normal appearing GOJ or a CLO <1cm the prevalence of IM was 24.3%, whereas, in the THP population, patients with dyspeptic symptoms and normal appearing GOJ the IM rate was zero (22, 23). Furthermore, in the USC population when the CLO was >! cm the rate of IM was 89% and in the THP population this was 22.4% (22,23). This indicates that in populations with high prevalence of GORD even endoscopically normal appearing GOJs are significantly damaged at microscopic levels and could harbor IM, whereas low GORD populations like ours endoscopically normal GOJs are less damaged and less likely to harbor IM.

In another study we carried out in the USC population, we demonstrated that 88.6% of GOJ adenocarcinoma and 89.6% of cardia adenocarcinoma are not associated with any gastric pathology and were negative for H. pylori (24). Further evidence to this effect has been published by others (25). This indicate that GOJ and cardia carcinomas are likely to be of oesophageal origin and arising from short or ultrashort segments of Barrett Oesophagus, i.e. IM. This raises the possibility whether what we perceive as "gastric cardia" is actually the distal oesophagus which is dilated due to loss of LOS tone and is a manifestation of GOR. It is well established by monomeric studies that in GORD, LOS has reduced or no tone depending on the severity of the disease.

Chandrasoma et.al. in a study of 10 oesophagectomy specimens, from the USC population, with normal appearing GOJ and proximal stomach, demonstrated that in the region corresponding to the "gastric cardia", lined by CM±OCM±IM, a length of 0.31cm to 2.05 cm had oesophageal markers such as submucosal glands and ducts. This indicates that what is seen as cardia in these cases are indeed dilated distal oesophagus (26). In the THP population, we analyzed 23 oesophagectomy specimens without a CLO. Of them 22 had CM ±IM associated with oesophageal markers in the region corresponding to cardia. This indicate, even in persons with less severe GOR damage, what we perceive as "gastric cardia" is oesophageal and occurs early in the disease process. We carried out another study on 714 patients with GORD, without a visible CLO, in the USC population; biopsies were obtained from GOJ, cardia (tips of proximal gastric rugal folds) and gastric body and antrum. Of them 643 had CM ± IM (90%, IM rate was 22.5%) and all biopsies had chronic inflammation. Of these a gastric pathology *(H. pylori* infection or atrophy with or without IM) was observed in only 9.9% and in the rest of there was no gastric pathology (27). Hence, this data did not reveal any association between chronic inflammation in the cardia with the rest of the stomach. This further indicates the pathological changes in the cardia are not related to gastric and probably of oesophageal origin. All these data indicate that the region we recognize as "gastric cardia" is not gastric but the dilated distal part of

the oesophagus due to GOR damage. With the damage of LOS and resultant reduced or loss of tone, under the relative negative intra-abdominal pressure, the intraabdominal part of the oesophagus dilates assuming gastric contours. When this segment gets lined by metaplastic glandular epithelium, it is impossible to differentiate it from gastric macroscopically (27,28).

Based on the assumption that cardia is gastric, it was believed that CM is a normal glandular mucosa in the proximal most stomach but could also occur as a metaplastic epithelium in the oesophagus. Chandrasoma and colleagues have proposed, based on endoscopic mapping biopsy studies and autopsy studies, that CM and IM at the GOJ region are always metaplastic and of oesophageal origin due to GORD, (26,29 -32). To prove this theory, we conducted a study in the THP population to assess the association of CM and IM in the GOJ region with oesophageal markers. Apart from submucosal glands and ducts, we also used multilayered epithelium and squamous islands within glandular mucosa as oesophageal markers (33-39). To further highlight these structures we used immunohistochemistry, namely P63 and 34E12. In 46 dyspeptic patients with a CLO or inflamed GOJ, 88% of CM±IM were associated with one or more oesophageal markers (40). In 112 dyspeptic patients without a CLO and normal GOJ, there were 35 cases with CM and of them 86% had associated oesophageal markers. In the THP oesophagectomy study, where there was no CLO in any specimen, all 23 cases had CM and of them 22 were associated with oesophageal markers. All this evidence indicates that even in macroscopically normal GOJ region CM is quite prevalent and if adequate criteria are used, in large majority of cases their metaplastic nature and oesophageal origin can be confirmed. Hence, the dilated distal oesophagus, giving the illusion of gastric cardia, is an early manifestation of GOR and is a common finding.

As stated above, epidemiologically, adenocarcinoma of the lower oesophagus, GOJ and cardia show a rising pattern, whereas, the distal gastric adenocarcinoma incidence is declining (20,21). This indicate that the gastric adenocarcinoma has a different aetiology from the former three categories. Clinical studies also have shown similar clinical behavior of distal oesophageal, GOJ and cardia adenocarcinoma (41,42). The main aetiological agent of Gastric adenocarcinoma is chronic *H. Pylori* infection (25). To demonstrate that adenocarcinoma of oesophagus, GOJ and cardia have no association with chronic *H. Pylori* infection we conducted a study, in the USC population, comprised 107 distal oesopahgeal adenocarcinoma, 79 GOJ adenocarcinoma and 48 cardia adenocarcinoma. All had simultaneous biopsies taken from the gastric body and antrum. In distal oesophageal adenocarcinoma 12.2% had gastric *H. pylori* infection and 82.2% did not have any gastric pathology. Similarly, in GOJ adenocarcinoma 5% had gastric *H. pylori* infection and 88.6% were without any gastric pathology; in cardia adenocarcinoma group 4.2% had *H. pylori* gastritis while 89.6% did not have any gastric pathology. Accordingly, oesophageal, GOJ and cardia adenocarcinoma did not show a positive correlation with any gastric pathology. This further supports that the adenocarcinoma of these three locations are more likely to be due to GORD and not related to a gastric pathology (24).

In conclusion, GOJ cannot be reliably identified endoscopically due to highly prevalent GOR related damage in this region, this is especially applicable in regions with high prevalence of GORD. The “gastric cardia” is proven to be of oesophageal origin and is due to dilated distal oesophagus as a result of damaged LOS. Dilated distal oesophagus appear to be an early manifestation of GOR, since many without a visible CLO had it. Furthermore, CM appear to be a metaplastic epithelium of oesophageal, rather than a normal epithelium in the proximal stomach. Therefore, GOJ can only be reliably detected microscopically, and is the junction between the squamous epithelium and gastric oxyntic mucosa; CM ±IM in between them are metaplastic and is called squamo-oxyntic gap. Presence of a squamo-oxyntic gap microscopically indicate GOR related damage.

Author declaration

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