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Gastroesophageal reflux disease. Are we acting in the best interest of our patients?

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Abstract. **Oesophageal adenocarcinoma is strictly related to gastroesophageal reflux and cylindrical metaplasia of the epithelium of the distal esophagus (Barrett's esophagus) due to chronic inflammation. Worldwide incidence of oesophageal adenocarcinoma is rising despite the availability of precise international guidelines for the treatment of gastroesophageal reflux disease and the increasing use of proton-pump inhibitors (PPIs). While PPIs can control GERD symptoms in a significant amount of cases, still a large number of patients progress to Barrett's esophagus and adenocarcinoma. Recent investigations have demonstrated that in one-third of the patients their reflux symptoms are due to non-acid reflux, obviously not affected by PPIs. Robust evidences are available to demonstrate the role of non-acid reflux in the development of Barrett's esophagus and adenocarcinoma. Therefore, PPIs are not effective in preventing the worst complications of GERD. It is mandatory to develop new and more effective guidelines on the treatment of GERD; that would take into account the fact that GERD should be considered a "surgical" disease, as it is due, at least in its late stages, to an anatomical defect of the lower oesophageal sphincter.**

Medical treatment should be considered in early stage GERD, when reflux is due to transient relaxations of the lower oesophageal sphincter, whereas surgery should be considered in late stages, in the presence of a demonstrated mechanical failure of the sphincter.

Key Words

Gastroesophageal reflux disease, Antireflux surgery, Proton-pump inhibitors, Barrett's esophagus, Esophageal adenocarcinoma.

Introduction

Gastroesophageal reflux disease (GERD) has been defined as "a condition which develops when the reflux of gastric content causes troublesome symptoms or complications"[1]. It is the single most common disease of the foregut in the western society. Its incidence is rapidly growing and so are its complications, mainly gastric metaplasia of esophageal mucosa (Barrett's esophagus) and esophageal adenocarcinoma.

The overall incidence of the most frequent types of esophageal cancer – squamous cells carcinoma and adenocarcinoma – has been increasing in the UK and worldwide since the mid-70s[2]. Esophageal adenocarcinoma tends to arise from Barrett's esophagus, that is columnar metaplastic epithelium of distal esophagus replacing the normal squamous epithelium as a response to chronic inflammation due to gastroesophageal reflux. Patients with Barrett's esophagus have a 50-100 times increase in their lifetime risk of esophageal cancer with respect to non-Barrett's individuals. The global risk of esophageal adenocarcinoma in patients with Barrett's is 186-1449/100,000 and tends to increase with time after diagnosis of Barrett's[3,4].

Also, the occurrence of Barrett's esophagus itself is increasing. VanSoest et al[5] reported an increase of occurrence of Barrett's in the Netherlands from 19.8 cases on 1000 upper GI endoscopies in 1997 to 40.5 in 2002. Similarly, the incidence of esophageal adenocarcinoma increased in the same period from 1.7/100,000 in 1997 to 6/100,000 in 2002.

Chronic treatment to reduce gastric production of acid is pivotal in trying to prevent formation or progression of Barrett's esophagus. The classic therapy with H2-receptors antagonists (H2ras) has been replaced, in the last decades, by treatment with the more effective proton pump inhibitors (PPIs).

Unfortunately, while H2ras/PPIs can control reflux symptoms in the majority of patients, they don't seem to yield any positive effect in reducing the risk of gastric metaplasia and malignant transformation of the distal esophageal mucosa. In fact, from the above-reported data, it seems that GERD as a predisposing factor to Barrett's and adenocarcinoma of the esophagus is not yet well controlled with medical treatment, despite the growing use – and maybe abuse – of PPIs and the significant public expenditure related to them.

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According to some reports, PPIs are the third most prescribed medications in the US, with 13.9 billion dollar sales per year[6].

We have searched the literature to try to find a possible explanation for this apparent inconsistency. Worldwide guidelines have been analyzed, in particular, those from UK, Europe and US, as in the Eastern world the incidence of esophageal cancer may be linked to different social and genetic factors.

As the widespread use of H2ras/PPIs is not able to control the increasing occurrence of GERD complications, it means that (1) our knowledge of GERD is biased or incomplete and/or (2) our guidelines on the treatment of GERD are not yet perfect or evidence-based and/or (3) our evidence-gaining methodology is still failing.

A new approach to GERD and its complication should be identified and implemented as soon as possible on a wide scale, in order to be able to revert the increasing trend of incidence of Barrett's esophagus and esophageal adenocarcinoma.

Review

According to the above reported Montreal definition[1], GERD can cause classical non-complicated esophageal syndromes (typical reflux symptoms, chest pain), complicated esophageal syndromes (with oesophagitis, Barrett's esophagus, stricture and adenocarcinoma) and extra-esophageal syndromes (with upper and lower respiratory and ear/nose/throat symptoms).

The cause underlying GERD symptoms is an established or transient lower esophageal sphincter (LES) failure.

LES was first described manometrically by Fyke and Code in 1956[7]. They demonstrated the presence of an intra-esophageal high-pressure zone just across the diaphragm. More recent 2D and 3D high-resolution manometry yield a better anatomo-functional idea of the LES.

Zaninotto et al[8] demonstrated that sphincteric failure occurs when LES pressure is lower than 6 mmHg, LES total length is less than 2 cm and LES abdominal length is less than 1 cm. When all three abnormalities are present, 92% of patients have reflux, confirmed by a 24h pHmetry.

This is clearly due to the anatomical failure of the LES.

Oddly, many patients with manometrically normal sphincter still complain of occasional reflux symptoms. Dodds et al[9] found that this is due to "transient LES relaxations" (TLRs), where the LES simply relaxes in response to a nervous reflex arch[9,10] or simply to gastric distension[11].

It has been lately observed that an anatomically defective sphincter is associated with supine or bi-positional reflux symptoms and esophagitis in the late stages of GERD, whereas TLRs are the cause of early stages GERD, mostly postprandial, in the upright position and with no esophagitis[12,13].

A hiatus hernia is most often associated with a defective sphincter[12].

Classically, the treatment of GERD is with PPIs proton-pump inhibitors (PPIs) or H2-receptors antagonists (H2ras). Unfortunately, more than 20% of GERD patients do not respond to PPIs or H2ras[14].

This is not due to odd pharmacokinetics, but simply to the fact that in those patients gastroesophageal reflux is not acid[15], as it has been clearly demonstrated by multichannel intraluminal impedance monitoring. In those patients, PPIs are not effective and expectantly they simply turn acid reflux into non-acid reflux[15,16], with no effect on the underlying mechanism of GERD.

Non-acid reflux is mostly alkaline, due to duodeno-gastric biliary reflux (DGBR). In the case of DGBR associated with LES failure, the esophagus is exposed to the effect of bile. It has been clearly proved that biliary reflux can be associated with increased risk of Barrett's transformation and esophageal adenocarcinoma[17-20].

Current guidelines on the treatment of GERD still give a central therapeutic role to PPIs and H2ras[21,22], thus addressing only about 70% of GERD-related issues. In particular, the American College of Gastroenterologists clearly states that there is no role for sucralfate or any other membrane-protectors. On the contrary, they may be considered the only real medical protection available against biliary reflux. Antireflux surgery is recommended in patients who respond to PPIs, that is only in patients with acid reflux[21,22]. Apparently, current guidelines do not address the issue of non-acid reflux, the one that is most directly related to Barrett's and adenocarcinoma.

It has been demonstrated that antireflux surgery re-establishes the function of the LES[13,23-25], prevents TLRs[26] and gives a better quality of life[27-29]. It can prevent progression of Barrett's and even downstage it[30-33], thus reducing the risk of esophageal adenocarcinoma.

Clearly, the surgical risk must be taken into account when considering surgery. The mortality rate is definitely low (less than 1%) and morbidity

rate is 8-17%[34]. These are acceptable figures provided that the correct indications for surgery are followed and a precise surgical technique is used.

Conclusions

Robust evidences suggest that (1) gastroesophageal reflux disease is due to an anatomical failure of the LES or to TLRs; (2) in about 1/3 of cases gastroesophageal reflux is not-acid; (3) PPIs/H2ras treatment is not effective on non-acid reflux; (4) non-acid reflux is associated with Barrett's and adenocarcinoma of the esophagus; (5) antireflux surgery is the only real treatment of GERD as it is able to restore LES function, thus preventing acid and non-acid reflux, improving patients' quality of life and reducing the risk of Barrett's and adenocarcinoma.

Are we pursuing the best interest of our patients with our current practice in the treatment of GERD?

The above-reported evidence may suggest that the answer to this question is "no", as we are treating with a medical therapy an anatomical disease, whose best treatment should be surgical.

Clearly, surgical risk and morbidity must be taken into account and one size doesn't fit for all.

An interesting proposal would be to consider medical treatment with PPIs, H2ras and membrane-protectors in patients with reflux symptoms but without esophagitis or an easily healable esophagitis and no manometric or clinical evidence of LES failure (upright or postprandial reflux). Control of symptoms in these patients can be improved by the oral administration of combination of hyaluronic acid and chondroitin-sulphate[35]. Surgery should be reserved to those patients with persistent esophagitis or GERD complications (Barrett's, stricture) and defective LES (supine or bipositional reflux symptoms, more than 1 component of LES defective at manometry).

Conflict of interest statement

Giovanni Domenico Tebala has no conflict of interest of any kind to disclose. In particular, Giovanni Domenico Tebala does not have any academic interest or any personal history that may hamper the conclusions of this work.

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