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Long-Term Acid Suppressive Therapy among Naïve Patients with *Mycobacterium Tuberculosis* Infection

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Abstract

Background/Aim: Our research hypothesis is that long-term acid suppression can lead to higher susceptibility to Mycobacterium tuberculosis infection due to defective gastric acid barrier. Our study aim was to determine the prevalence of long-term acid suppressive therapy use among patients with Mtb infection and to explore its contribution to the development of infection.

Patients and Methods: A case-control study included 264 patients with newly diagnosed, pulmonary or extrapulmonary TB, consecutively, and an equal number of normal subjects as a control group. For all the enrolled, clinical evaluation (medical history and physical examination), abdominal ultrasonography, chest radiography, and laboratory evaluation were provided. Long-term use of acid suppressive therapy was defined as the use for three months or more, during the year preceding the diagnosis of TB.

Results: The study groups were matching regarding age and gender. The most frequent type was pulmonary TB (65.2%). Omeprazole was the most frequently used acid suppressive agent (39.6%). Factors associated with Mtb infection were diabetes mellitus, chronic obstructive pulmonary disease, long-term corticosteroids use, long-term acid suppressive therapy, liver cirrhosis, renal failure, and congestive heart failure. After adjusting for the cofounding variables, long-term acid suppressive therapy had adjusted or of 2.1 (95% CI 1.4-6.1; p 0.024) for its use among the study cases.

Conclusions: In conclusion, the wide use of acid suppressive therapy for long durations (especially PPI) can make the patients more vulnerable to infection with Mtb.

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Introduction

The Gastric acid plays a major role in decontamination of the upper gastrointestinal tract. One of the major factors controlling bacterial distribution in gastrointestinal tract is the gastric acid barrier, which may be affected by using inhibitors of gastric acid secretion, gastrectomy, dietary indiscretion, and stress [1]. Following the widespread use of long-term acid suppressive therapy for treatment of Peptic Ulcer Disease (PUD) and Gastroesophageal Reflux Disease (GERD), elimination of the acid barrier was accused for its association with several infectious diseases [2]. Being available for long time, Proton Pump Inhibitors (PPI) is linked to enteric infections, such as *Clostridium diffcile* colitis [3], *Salmonella enteritis* [4] and spontaneous bacterial peritonitis in patients with advanced cirrhosis [5]. Moreover, patients using PPI are at increased risk of both nosocomial and community-acquired pneumonia, while the contribution of Histamine-2 Receptor Antagonists (H2RA) was controversial [6,7].

Among the different respiratory tract infections, (Mtb) infection is still an important public health problem in the developing countries. With the latent and indolent phases and the emergence of drug resistance [8], the resurgence of Tuberculosis (TB) is a global problem [9]. The prevalence of Mtb infection is higher among patients who have undergone gastrectomy, which is a risk factor for the development of TB [10,11]. Recent use of acid suppressive therapy is associated with both infection and activation of TB [12]. Patients with GERD are at increased risk of pulmonary TB due to the long-term use to PPI [13].

Table 1: Types of TB among the study cases (n = 264).

Pulmonary TB	172 (65.2)
Pleural TB	43 (16.3)
Peritoneal TB	36 (13.6)
Intestinal TB	9 (3.4)
Renal TB	4 (1.5)
TB: tuberculosis; n: number; (percent).	
Data are presented as frequency (percentage).	

Table 2: Relative frequency of using acid suppressive agents among the study population (n=528).

Omeprazole	209 (39.6)
Pantoprazole	140 (26.5)
Famotodine	115 (21.8)
Rabeprazole	84 (15.9)
Esomeprazole	67 (12.7)
Lanzoprazole	48 (9.1)
Ranitidine	43 (8.1)
n: number; (percent). Data are presented as frequency (percentage).	

Our research hypothesis is that long-term acid suppression by PPI can lead to higher susceptibility to Mtb infection due to defective gastric acid barrier. Our study aim was to determine the prevalence of long-term acid suppressive therapy use among the patients with Mtb infection, and to explore its contribution to the development of infection.

Patients and Methods

Study design

A hospital-based case-control study was carried out.

Study location

The study population was recruited from the patients attending the outpatient clinics and the inpatient sectors of the department of Chest Diseases and Tuberculosis, department of Tropical Medicine and Gastroenterology, and department of Internal Medicine.

Study duration

The study population was recruited during the period from June 2015 to September 2017.

Inclusion criteria

Our study population included 528 subjects; 264 cases with newly diagnosed TB (pulmonary or extrapulmonary), and 264 normal subjects after exclusion of Mtb infection.

Exclusion criteria

Pregnant patients, patients less than 18 years old, and those using alcohol during the previous eight weeks before enrollment were excluded from the study. Also, excluded from being enrolled were patients with history of gastric surgery and neoplasms.

Methods

For all the enrolled, clinical evaluation (medical history and physical examination), abdominal ultrasonography, chest radiography, and laboratory evaluation were provided. Long-term use of acid suppressive therapy was defined as the use for three months or more during the year preceding the diagnosis of TB, while long term corticosteroids use was defined as use of any dose of oral or parenteral corticosteroids for more than one month during the same year.

Pulmonary TB was diagnosed based on positive microscopy of smear from sputum or bronchoalveolar lavage using hot carbol fuchsin method (Ziehl-Neelsen) and/or positive sputum or bronchoalveolar lavage culture on solid medium (Löwenstein-Jensen) [14]. Pleural TB was diagnosed based on positive histopathologic examination or culture of pleural tissue sample obtained by thoracoscopy and/or positive microscopy of smear from pleural fluid. Tuberculous peritonitis was diagnosed based on positive histopathologic examination or culture of peritoneal tissue sample obtained by laparoscopy and/or positive microscopy of smear from ascitic fluid. Tuberculous enteritis was diagnosed based on positive histopathologic examination or culture of terminal ileum mucosal sample obtained by colonoscopy. Renal TB was diagnosed based on positive histopathologic examination or culture of renal tissue sample obtained by ultrasonography-guided renal biopsy [15].

Laboratory investigations included estimation of the fasting serum level of glucose, serum level of creatinine, liver chemistry, complete blood count, and testing for Human Immunodeficiency Virus (HIV) antibodies.

Statistical analysis

Data were analyzed using the Statistical Package for Social Sciences (IBM SPSS Statistics, version 22.0, release 22.0.0.0; IBM Corp) for Microsoft Windows® (64-bit version). Results were expressed as mean ± standard deviation or frequency (percentage) as appropriate. Student's t-test or Mann-Whitney U test, and Yates' corrected chi-squared test or Fischer's exact test as appropriate were used to compare the variables between the study groups. A p value less than 0.05 was considered statistically significant. The adjusted odds ratio (OR) with 95% Confidence Interval (CI) of exposure for cases compared with control subjects were estimated using logistical regression. Risk factors in univariate analyses found to modify the OR for the association between acid suppressive therapy and Mtb infection by at least 5% were included in a multivariate model. Multivariate analysis was used to adjust for the confounding factors, identifying the association between long-term acid suppressive therapy and Mtb infection.

Power analysis of the performed chi-square tests was done using the G*power software version 3.1.9.2. A power of 84% was achieved to detect a medium sized effect. Plotting power against various effect size values showed reasonable power values for medium and large effect sizes. However, for detection of small effect size, the test appeared to be underpowered.

Ethical considerations

The study was conducted after approval of the Clinical Research Ethical Committee of Assiut Faculty of Medicine and was carried out according to the code of ethics of the World Medical Association (Declaration of Helsinki). All the participants signed a consent certificate after discussing in detail with the investigators the certificate subjects and the study aim. Participants were clearly informed that refusing to participate in the study will not affect having full benefit of the available medical service. Data confidentiality was respected.

Results

The study included 264 patients with Mtb infection as cases (mean age of 45±15.4 years; 59% were males) and 264 normal subjects as a control group (mean age of 43±12.7 years; 54% were males).

Table 3: Indications of long term acid suppressive therapy among the study population with long term acid suppressive therapy (n = 80; 57 cases and 23 normal subjects).

GERD	**54 (67.5)**
PUD	13 (16.3)
Functional dyspepsia	7 (8.7)
Prophylactic use (on long term NSAID or corticosteroids therapy)	6 (7.5)

n: number; GERD: gastroesophageal reflux disease; PUD: peptic ulcer disease; NSAID: nonsteroidal anti-inflammatory drugs
Data are presented as frequency (percentage).

Table 4: Demographic and clinical characteristics of the study population.

	Cases (n = 264)	Controls (n = 264)	OR (95% CI)	p-value
DM	76 (28.8)	31 (11.7)	2.7 (1.6-5.3)	0.009 *
Chronic obstructive pulmonary disease	69 (26.1)	40 (15.2)	1.9 (1.5-4.8)	0.011 *
Long term corticosteroids use	60 (22.7)	15 (5.7)	3.9 (2-8.4)	0.003 *
Long term acid suppressive therapy	57 (21.2)	23 (8.7)	2.1 (1.4-6.1)	0.024 *
Liver cirrhosis	43 (16.3)	20 (7.6)	1.8 (1.2-7.2)	0.036 *
Renal failure	31 (11.7)	11 (4.2)	2.3 (1.7-9.4)	0.020 *
Congestive heart failure	24 (9.1)	16 (6.1)	1.7 (1.3-11.9)	0.028 *

n: number; (percent); OR: adjusted odds ratio; CI: confidence interval; DM: diabetes mellitus.
Data are presented as frequency (percentage).
*Statistically significant.

Table 1 shows the different types of TB among the study cases; the most frequent type was pulmonary TB (65.2%). Different agents used for long-term acid suppression by the study population are shown in Table 2 omeprazole was the most frequently used agent (39.6%). More than one acid suppressive agentwas used, either simultaneously or consecutively. Table 3 shows the indications for long-term acid suppressive therapy among the study population. The most frequent indication was GERD (67.5%). Regarding the potential adverse effects of the long-term use of acid suppressive therapy; 8.7 % of the study population reported episodes of diarrhea (less than one-week duration), and 3.4 % reported episodes of bone pain.

The demographic characteristics and clinical characteristics of the study population are presented in Table 4. None of study population had human immunodeficiency virus infection. Among the cases, 28.8% had Diabetes Mellitus (DM), including 9.1% with uncontrolled DM. Liver cirrhosis was detected among 16.3% of the cases; it was decompensated among 11.4% of them. The etiology of congestive heart failure detected among 9.1% of the cases was coronary heart disease in 21 out of 24 patients (87.5%), rheumatic heart disease in 2 (8.3%), and while the etiology was unknown in one patient (4.2%). Factors associated with Mtb infection were DM, chronic obstructive pulmonary disease, long term corticosteroids use, long term acid suppressive therapy, liver cirrhosis, renal failure, and congestive heart failure. After adjusting for the cofounding variables, long term acid suppressive therapy had adjusted OR of 2.1 (95% CI 1.4-6.1; p 0.024) for its use among the study cases.

Discussion

In addition to the other comorbidities, it was found that long term acid suppressive therapy was associated with increased risk of Mtb infection after adjusting for the confounding factors. This result agreed with Hsu, et al, who reported association of Mtb infection with the long-term use of acid suppressive therapy (PPI and H2RA), in addition to other comorbidities [12]. In addition to the association of TB with the use of acid suppressive therapy, they reported the association of Mtb infection with PUD and GERD. Although their study included a larger sample size compared to ours, we had the advantage of prospective inclusion of the study population, and not relying on retrospective collection of data. However, another study reported no association between gastrointestinal TB and long-term use of PPI [16]. This can be explained by being limited to gastrointestinal TB, lacking the inclusion of patients with pulmonary TB or other forms of extrapulmonary TB.

Gastric acid keeps the environment acidic inside the stomach, which inhibits bacterial growth except for *Helicobacter pylori* [17]. When gastric acid secretion decreases, the drop of gastric acidity leads to a defect of its protective mechanism and consequently, ingested bacteria can survive and proliferate inside. This applies also to the pathogens causing pneumonia. Several studies reported a higher possibility of developing community-acquired pneumonia among the patients on long-term acid suppressive therapy. However, long-term acid suppressive therapy is surpassed by more important risk factors of pneumonia such as aging, immune suppression, and comorbidities [6,18,19].

There is some degree of overlap between the risk factors of Mtb infection and those of community-acquired pneumonia; they include DM, aging, HIV infection [20]. Gastrectomy is considered as a risk factor of Mtb infection [21], as it leads to malnutrition and consequently immune suppression. Long-term proton pump inhibitors therapy is associated with micronutrient deficiencies, especially of iron and vitamin B12 [22].

The inability to accurately estimate the dose or duration of acid suppressive therapy use is considered as a limitation; the estimation of duration was approximate. In addition, lack of data regarding Mtb lineages/sublineages is considered another limitation.

In conclusion, despite being invaluable therapy for many alimentary tract diseases as GERD and PUD, the wide use of acid suppressive therapy for long durations (especially PPI) can make the patients more vulnerable to infection with Mtb. Further larger scale, prospective studies are recommended before considering screening for Mtb infection among patients on long-term acid suppressive therapy.

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