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Original research article

# Does hiatal hernia impact gastroesophageal reflux-related chronic cough?

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Title: Does hiatal hernia impact gastroesophageal reflux-related chronic cough?

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Take home message

Assessing the presence and size of hiatal hernia in chest CT may be helpful in the management of adults with gastroesophageal reflux-related chronic cough, as it may be related with worse response to anti-acid treatment and impact the severity and duration of chronic cough.

## Abstract

Hiatal hernia (HH) may coexist with gastroesophageal reflux-related chronic cough (GER, CC). The study aimed to evaluate whether the presence of HH was related to CC severity and the response to anti-reflux therapy.

This was a retrospective analysis of data on adults with GER-related CC managed in our cough center between 2017 and 2021. Patients who had undergone chest CT and in whom follow up data were available were included. The presence and size of HH were assessed based on thorax CT scanning. Patients were treated with modification of diet and proton pump inhibitors. The response to treatment was assessed by the change in quality of life (QOL) measured by Leicester Cough Questionnaire (LCQ) and cough severity was measured by 100

mm Visual Analogue Scale (VAS).

Forty five adults (28 F, 17 M) were

included. HH was demonstrated in 12 patients (26.6%). Patients with HH did not differ from those without HH in clinical characteristics, cough duration and severity, and cough-related QOL. We found moderate positive correlations between maximal sagittal diameter of HH and cough severity ( $\rho=0.692$ ,  $p=0.013$ ) and duration ( $\rho=0.720$ ,  $p=0.008$ ).

Patients without HH responded better to anti-reflux therapy with significant LCQ improvement. A strong negative correlation between sagittal diameter of HH and increase in LCQ ( $\rho=-0.764$ ,  $p=0.004$ ) was demonstrated.

The presence of HH identified in chest CT may impact cough severity, duration and response to anti-reflux treatment in patients with GER-related CC. Further prospective studies are justified to confirm significance of HH in the management of CC.

## Key words

Hiatal hernia, chronic cough, gastroesophageal reflux disease, chest imaging

## Introduction

Gastroesophageal reflux (GER) is regarded as the third most common cause of chronic cough (CC) in adults, following asthma (A) and upper airway disorders [1-3]. The prevalence of GER-related CC ranges from 1.4 to 85.4% with lower values reported in Asia and higher in Europe and North America [1]. The diagnosis of GER-related CC is usually based either on the coexistence of CC and typical symptoms of GER such as heartburn, regurgitation, and belching or on the evidence for GER in imaging studies and esophageal function tests (esophageal pH-monitoring with/without impedance and esophageal manometry, barium swallow test or endoscopy) and alleviation of cough after anti-reflux therapy in a patient with CC [1-4]. According to the first *American College of Chest Physicians* (ACCP) guidelines GER-related CC might be highly suspected in the proper clinical context after exclusion of other potential causes of CC [2,5]. The therapeutic approach to GER-related CC is similar to that recommended in gastroesophageal reflux disease (GERD) with predominating esophageal symptoms and usually commences with diet modification, promotion of weight loss in obese and overweight patients, avoiding meals within three hours before bedtime and bed elevation during rest and sleep [5]. The next step of treatment in patients with typical GERD symptoms includes anti-acid therapy with proton pump inhibitors (PPI), H<sub>2</sub> antagonists or alginate for at least 8 to 12 weeks [5]. If response to treatment is unsatisfactory, prokinetic drugs may be considered. In contrast, PPI therapy is not recommended in patients with CC and suspicion of GER who have no heartburn or regurgitation [4,6,8]. Anti-reflux surgery may be considered in highly selected symptomatic patients with confirmed acid GER-related CC, inadequate response to at least 3 months of anti-reflux therapy and exclusion of esophageal dysmotility. Importantly, the risk of surgery-related complication is not negligible [7,8]. Despite various treatment modalities, one randomized controlled trial revealed that the result of causal treatment in GER-related CC is highly unsatisfactory and leads to significant cough reduction in only 12.5-35.8% of patients [9].

GER is a consequence of increased relaxation of the lower esophageal sphincter (LES). Hiatal hernia (HH) may be a predisposing factor for GER as it leads to separating LES and the crural diaphragm, thus decreasing their ability to cooperate as a barrier to reflux events [10,11]. Sliding HH larger than 2 cm in size is considered to be a clinically important mechanism for GER [5,12].

The barium swallow test and esophagoscopy have been the classic methods for HH diagnosis, but recently thoracic and abdominal computed tomography (CT) is also considered a reliable tool for the diagnosis and evaluation of HH [11]. HHs are identified on non-contrast CT of the chest as a proximal displacement of the esophagogastric junction of the diaphragm into the mediastinum through the esophageal hiatus. Besides documenting the presence of HH, there has been an

emerging interest in the measurements of hiatus size, as it may have clinical implications in patients who require fundoplication surgery [11,13].

As HH is not a rare finding in thoracic CT, this study aimed to analyze whether the presence of HH in thorax CT was related with more severe cough and worse response to anti-reflux therapy in adults with GER-related CC treated in our cough center.

The study protocol was approved by the Institutional Review Board of the Medical University of Warsaw (KB/101/2009) as a part of a larger project on the efficacy of CC management. All patients signed an informed consent to analyze results of their diagnostic tests and management for research purposes. The research was conducted according to the principles of the World Medical Association Declaration of Helsinki.

## **Methods**

### *General study design*

This study was designed as a retrospective analysis of data on selected adults with CC and GER managed in the cough center of the Department of Internal Medicine, Pulmonary Diseases and Allergy Medical University of Warsaw between 2017 and 2021.

### *Patients and definitions*

CC was defined as cough lasting for more than 8 weeks. The study included patients with CC and GER, in whom thoracic CT was performed as an element of integrative CC diagnosis work-up and the response to anti-reflux treatment was documented (Figure 1). Patients with other coexisting cough causes were also included; surgical treatment for GER was an exclusion criterion.

GER was diagnosed in adults with CC and either typical symptoms of GER or the results of esophageal impedance/pH-monitoring or gastroscopy suggesting GER. HH was diagnosed based on the assessment of thorax CT scans. The initial treatment of GER included modification of diet, lifestyle and PPI - either omeprazole 40 mg bid or pantoprazole 40 mg bid for 4-6 weeks. If the patient did not respond to the initial anti-reflux therapy, the treatment was enhanced by adding prokinetic drugs.

Cough severity and its impact on quality of life were measured by 100 mm Visual Analogue Scale (VAS) and cough-related quality of life questionnaire was assessed by the Leicester Cough Questionnaire (LCQ), respectively [4,14]. Response to GER therapy was measured by comparison of cough severity and quality of life before and after 4-6 weeks of treatment. Improvement in LCQ of more than 1.3 points was used as the criterion to distinguish responders and non-responders to therapy [14].

### *Thorax CT acquisition and assessment*

All thorax CT scans were performed at peak inspiration using spiral mode of 64-row multidetector CT scanner (Optima CT660; General Electric HealthCare, Chicago, Illinois, United States). The acquired CT data of patients with GER-related CC were analyzed by one radiologist (JZ) blinded to the details of patients' clinical characteristics. Multiplanar reconstruction (MPR) of each CT was performed using AW Server (GE Healthcare United States). Axial images of 1.25 mm thickness in soft tissue algorithm were loaded into a standard multiplanar reformat package, showing images in three orthogonal planes (axial, coronal and sagittal). In the oblique sagittal reformatted reconstruction an image through the esophageal hiatus was identified. Small adjustments in angle and position were performed to maximally demonstrate the margins of the hiatus and hernia. At this level, the distance between anterior and posterior margins of the esophageal hiatus (gate of the hernia; Figure 2a) and maximal anterior and posterior dimension of the hernia sac (maximal sagittal dimension) were measured (Figure 2b). The maximal hernia length (gastric folds extending above the diaphragm) was measured by drawing a perpendicular line up to the superior margin of the hernia (Figure 2a). In the coronal oblique reformatted reconstruction, after adjustment to show maximal coronal dimensions of the esophageal hiatus and hernia, the distance between right and left margins was measured (Figure 3a and 3b) [11,15-17].

### *Statistical analysis*

Descriptive statistics (median and interquartile range) were used to present patient demographics. Due to non-normal distribution of data, non-parametric tests were used for analysis. The differences between cough severity and quality of life before and after treatment were tested using Wilcoxon test. Various characteristics of responders and non-responders were compared using chi-square test for categorical variables and Mann Whitney U test for continuous variables. Spearman coefficient was used for correlation analysis. P value less than 0.05 was considered statistically significant.

## **Results**

GER was diagnosed in 109 of 285 adult patients (38.2%) referred to our cough center due to CC between 2017 and 2021. Among them, chest CT was performed in 74 patients as a component of routine diagnostic procedure. In 47 patients in this subgroup (29F, 18M), response to therapy was documented. Two patients who had undergone surgical treatment for HH (laparoscopic Nissen fundoplication) were excluded. Thus 45 patients were included in the final analysis (Figure 3). Among them, GER was diagnosed based on the presence of typical reflux symptoms (n=35), the results of 24-hour impedance and pH monitoring (n=8) and on the results of endoscopy (n=2).

HH was demonstrated in thorax CT scans of 12 patients (26.6 %), sliding HH (type I) being present in all cases. The median coronal and sagittal hiatus diameters were 21.5 mm and 20.5 mm. The median coronal and sagittal hernia diameters were 27.5 mm and 29.0 mm and the median hernia length was 29.5 mm, respectively. Patients with GER and HH did not differ from other GER patients in terms of clinical characteristics, cough severity or duration, cough related quality of life, efficacy of anti-reflux treatment with modification of diet and PPI (Table 1).

In both groups anti-reflux therapy was associated with reduced cough severity but only in patients without HH significant improvement in LCQ was observed (Table 2).

Among patients with CC due to GER and HH, strong positive correlations between the maximal coronal diameter of HH and baseline cough severity ( $\rho=0.692$ ,  $p=0.0126$ ) and baseline cough duration ( $\rho=0.720$ ,  $p=0.008$ ) were observed. Moreover, a strong negative correlation was found between the hiatus gate diameter and increase in LCQ following therapy with diet modification and PPIs ( $\rho=-0.737$ ,  $p=0.009$ ).

## Discussion

The results of our study suggest that the presence of HH may be related with worse response to anti-acid treatment in patients with GER-related CC and that the size of HH impacts the severity and duration of GER-related CC. According to our knowledge, there are very few studies concerning the impact of HH on GER-related CC. Thus, this observation may be valuable in context of limited efficacy of anti-reflux therapy in patients with GER related CC pointing to those patients, who may benefit from more intense anti-reflux therapy.

There have been numerous earlier studies demonstrating a relationship between the exposure of the distal part of the esophagus to non-acidic or acid content and the prevalence of CC [18-21]. Initially, researchers postulated that cough might be initiated by esophageal irritation by acidic refluxate, then an airway reflux hypothesis was proposed based on proximal reflux and microaspiration [22]. The airway reflux describes gaseous or liquid, weakly acidic or non-acidic refluxate, which ascends through the esophagus to the upper airways, what results in airway epithelium damage and stimulation of the cough reflex [22]. Esophageal dysmotility is increasingly frequently recognized in CC patients and it is regarded as an important contributor to the pathophysiology of airway reflux and cough hypersensitivity (4). HH has been shown to be closely related to reflux symptoms, reflux esophagitis, Barrett's esophagus and esophageal adenocarcinoma [12]. Besides, higher prevalence of esophageal dysmotility in patients with HH compared to subjects without HH was described [23,24] The potential pathomechanism of esophageal dysmotility is related to the decreased pressure of gastroesophageal junction due to displacement of lower esophageal sphincter and the diaphragmatic crura [25]. However, to our knowledge, the influence of

HH on CC has not been widely assessed before. In study by Schlottmann et al., patients with GER and larger HH presented with more frequent episodes of coughing and wheezing [26]. Similarly, the results of our study documented positive correlations between maximal coronal diameter of HH and cough severity and duration. However, the median HH length in our study was 29.5 mm (25– 32 mm), what suggests that HH detected in our investigated patients were rather small. Despite its small size, the presence of HH may impact the severity and duration of CC, as well as response to CC treatment. The increasing use of thoracic CT in the diagnostic work-up of adults with difficult to treat CC enables to assess the presence and size of HH. In our recent study, HH was the most common abnormality potentially related to cough found in thoracic CT in patients with no evident abnormality on plain chest X-ray (8/ 189, 4.2%) [27].

Although the efficacy of therapy with PPI in patients with CC is regarded as low, we started treatment with diet modification and short period trial of PPIs, as majority of our patients presented typical reflux symptoms. We found that coexistence of HH and GER-related CC may be associated with a worse outcome of such treatment. In an earlier study, Dickman et al. also found that HH was more common in patients who failed to respond to PPIs [28]. On the other hand, Hu et al. documented that PPIs did not improve esophageal dysmotility [29]. As HH may favor esophageal dysmotility, we suppose that patients with HH and CC may rather benefit from non-pharmacological methods and prokinetic drugs than PPIs. Recent guidelines emphasize different phenotypes and personalization in the management of GER and also may refer to the presence of HH [5,30,31]. If typical symptoms of GER and known HH coexist, non-pharmacological therapies (reduction of supine GER by elevating the head of the bed and avoiding meals within 3 hours before bedtime), alginates (to neutralize the acid pocket in HH) and considering surgical treatment seem justified [30,31]. We may assume that this may also apply to the presence of HH in patients with GER related CC, but further prospective studies are necessary to demonstrate if personalization of GER treatment leads to reduction of CC.

In the diagnosis of HH, upper gastrointestinal endoscopy, barium swallow radiography and esophageal manometry are gold standard investigations [12]. However, thoracic CT may also be considered as the one of the additional tests in diagnosis and measurement of HH [11,32]. Recently, few studies revealed presence of HH in thoracic CT in 40-53% of patients with idiopathic pulmonary fibrosis (IPF) [17,33] and 59% patients with scleroderma and pulmonary fibrosis. Moreover, HH was shown to be related with progression and mortality in IPF [17,34]. Worse airway disease severity was also documented in patients with non-cystic fibrosis bronchiectasis with coexisting HH [35].

The results of this study indicate that further research assessing the possible impact of HH on CC is justified.



We are aware about some limitations of our study. First, it was a retrospective study which included a limited number of patients burdened with risk of selection bias. Therefore our results need to be verified in a larger prospective cohort study. Second, we only analyzed patients with GER related CC and HH, so the significance of HH in other patients with CC needs further analysis. Third, we only analyzed effectiveness of life style and diet modification and anti-acid treatment, so further steps of anti-reflux therapies (prokinetic drugs, surgical treatment) still need precise evaluation. Furthermore, the analysis was performed in adults treated in our cough center, where mainly patients with difficult to treat CC are managed. Assessment of the treatment efficacy of GER-related CC was based on patient related outcomes without objective measurements such as cough monitors, which are not routinely used in our cough center. Finally, many of our patients with GER-related CC had also other cough causes, what might have influenced treatment efficacy. Despite these limitations, we believe that this real-life observation gives arguments for detailed assessment of HH in thoracic CT scans performed in patients with CC and justifies further prospective studies on the significance of HH in treatment of CC.

In conclusion, analysis of presence and size of HH in thoracic CT may be useful in patients with GER-related CC as HH might be related with longer, more severe GER-related CC and worse response to anti-acid treatment in these patients. Further prospective studies to confirm the findings of this study seem justified.

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### **Figure legends**

Figure 1. Flow chart presenting patient selection for the study.

Figure 2. Measurement of hiatal hernia in thoracic CT (sagittal oblique reformatted reconstruction).

Figure 2a. Measurement of gate (maximal distance between anterior and posterior margins of the esophageal hiatus) and length (gastric folds extending above the diaphragm) of hiatal hernia.

Figure 2b. Measurement of maximal sagittal dimension of hiatal hernia (maximal anterior and posterior distance).

Figure 3. Measurement of hiatal hernia in thoracic CT (coronal reformatted reconstruction).

Figure 3a. Measurement of maximal coronal dimension (maximal distance between right and left margins) of hiatal hernia.

Figure 3b. Measurement of gate of hernia (distance between right and left margins of the esophageal hiatus).

## Tables

Table 1.

Comparison of CC patients with and without hiatal hernia.

Patients' characteristics	Patients with GER and hiatal hernia N=12	Patients with GER without hiatal hernia N=33	P value
Age (years)	61.5 (53.5-70)	57 (45-68)	0.342
Gender F/M	8/4	20/13	0.585
BMI (kg/m <sup>2</sup> )	29.0 (27.0-32.4)	29.7 (25.9-32)	0.616
Cough duration (months)	66 (57-180)	48 (24-96)	0.079
Cough severity VAS (mm)	70.0 (55.0-78.0)	72.0 (51-80)	0.959
Cough related QoL (LCQ)	10.32 (8.9-12.3)	10.65 (7.955-12.70)	0.767
Coincidence of asthma/NAEB	5 (41.7%)	17 (51.5%)	0.587
Coincidence of UACS	5 (41.7%)	20 (60.6%)	0.263
Smoking history NS/ExS/S	100/2/0	21/11/1	0.182
Response to therapy (change in VAS)	-13.0 [(-45)-(-5.5)]	-9.0 [(-32)-4]	0.550
Response to therapy (change in LCQ)	1.42 [(-0.01) -3.16]	2.01 (0-4.4,4)	0.967
Responders to GER therapy	6 (50%)	17 (51.5%)	0.928

GER= gastroesophageal reflux, F= female, M= male, BMI= body mass index, VAS= visual analogue scale, QoL= quality of life, LCQ= Leicester Cough Questionnaire, NAEB= non-asthmatic eosinophilic bronchitis, UACS= upper airway cough syndrome, NS= nonsmokers, ExS= ex-smokers, S= smokers

*Data are given as median and interquartile range or number of patients and percentages. Mann-Whitney U test and chi square test were used for analysis.*

Table 2.

Detailed data on the response to therapy in patients with and without hiatal hernia.

	Before therapy	After therapy	P value
Patients with GER and hiatal hernia N=12			
VAS (mm)	70 (55-79)	41 (18-78)	0.029
LCQ (points)	10.32 (8.85 -13.26)	10.69 (8.92-13.81)	0.272
Patients with GER without hiatal hernia N=33			
VAS (mm)	72 (51-80)	43 (25-80)	0.007
LCQ (points)	10.65 (7.94-12.82)	12.36 (8.53-15.73)	0.002

VAS= visual analogue scale, LCQ= Leicester Cough Questionnaire, GER= gastroesophageal reflux

*Data are given as median and interquartile range. Wilcoxon test was used in analysis.*

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