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## **Chronic Cough and Obesity**

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## Abstract

With respective prevalence of 13% and 9.6%, obesity and chronic cough are two common conditions worldwide. The crucial role of obesity has been highlighted in the development and progression of many respiratory diseases. According to the results of epidemiological studies, obesity, particularly abdominal obesity, may also be associated with chronic cough (CC). CC seems to be more severe in obese patients compared to normal-weight subjects. The management of CC may differ slightly in obese patients compared to non-obese patients. Indeed, asthma and reflux diseases, which are considered key factors in the onset of CC, are characterised by more severe symptoms in obese patients. Asthma is associated with a resistance to usual treatments in obese patients but no data are available on the effect of inhaled therapies in obese subjects with cough variant asthma. Other emergent causes of CC have been reported in obese patients. Obstructive sleep apnoea and diabetes may also be involved in the development of CC and should be taken into account in obese patients with CC. The beneficial effect of weight loss on chronic cough has been suggested.

Key words: obesity, cough, asthma, GERD (gastroesophageal reflux disease).

## Introduction:

Obesity plays an important role in the development and progression of respiratory diseases. In asthma, obesity is considered a major comorbidity that exacerbates respiratory symptoms [1]. Many epidemiological studies have shown that obese patients have a higher risk of developing asthma than the general population demonstrating that obesity is involved in the development of asthma [2]. It is also well established that asthma associated with obesity is a phenotype with more difficult-to-treat asthma compared to non-obese subjects [3, 4]. Obesity also plays an important role in chronic obstructive pulmonary disease (COPD) because it is associated with worse COPD-related outcomes and specific management of obesity reduces the risk of acute exacerbation of COPD [5]. In many lung diseases, weight loss is required to improve respiratory symptoms.

Chronic cough is a common entity in respiratory medicine. It is a complex disorder, the management of which has recently been defined in the guidelines of the American College of Chest Physicians [6]. All the steps covering the investigations and initial treatments are detailed in these guidelines. However, body mass index (BMI) measurement and assessment of obesity markers are not included in the evaluation of patients with chronic cough. As with other respiratory diseases, should obesity be taken into account in the management of chronic cough? Does obesity impact on the development of chronic cough? In this review, the link between chronic cough and obesity will be discussed as well as the clinical approach to an obese patient with chronic cough.

## Epidemiological data on chronic cough and obesity

Over the last 40 years, obesity has tripled worldwide and is now considered a genuine public health problem [7]. In 2016, more than 1.9 billion people were overweight and more than 650 million were obese according to the World Health Organisation (WHO) [7]. Thirty-nine

percent (39%) of adults are overweight and 13% are obese, worldwide [7]. Overweight and obesity are significantly associated with morbidity and mortality rates and a high BMI accounts for 4.0 million deaths globally [8]. Cardiovascular diseases and cancer are particularly involved in the mortality of obese patients [9, 10]. Other diseases such as diabetes, hypertension, joint or digestive disorders are responsible for high morbidity rates in obese patients [11].

Chronic cough places high demands on health care systems but it is not classically associated with obesity. Chronic cough is a common disorder and its prevalence is estimated at 9.6% worldwide according to a meta-analysis [12]. In clinical practice, it is not surprising to observe the combination of two common diseases. However, is the association of chronic cough and obesity a coincidence or is there a link between these two disorders?

In their meta-analysis on the prevalence of chronic cough worldwide, Song *et al.* note that chronic cough is more frequent in Europe and America than in Asia and Africa [12]. The authors assume that comorbidities such as obesity might contribute to regional variability but this relationship was not examined in their meta-analysis. The guidelines on the management of cough in adults published in 2006 by Morice *et al.*, specify that chronic cough is reported by 10 to 20% of adults and this disorder is more common in female and obese subjects [13]. Indeed, in a cross-sectional study involving 4003 patients, obesity (defined by a BMI  $\geq 30$  kg/m<sup>2</sup>) was associated with cough with an odds ratio (OR) of 1.66 [99% CI (confidence interval) 1.19-2.32] in terms of univariate analysis. However, the difference was still not significant in the multivariate analysis, which suggests confounding factors [14]. More recently, Moralles-Estrella reported that patients with a higher BMI experience cough more often than other patients and the cough is more severe in obese patients [15].

BMI is a straightforward, easy-to-use marker but other obesity markers can also be used in clinical practice. Thus, waist-to-hip ratio seems to be more accurate in predicting

cardiovascular risk [16]. The effect of various risk factors such as abdominal obesity on chronic cough was assessed in a large population-based cohort study performed in Denmark involving 14,669 adults. Abdominal obesity, defined as waist-hip ratio  $> 0.85$  for women and  $> 0.90$  for men, was statistically more common in patients with chronic cough ( $n=554$ ) compared to healthy subjects (65% vs. 53%) [17]. In the total population, abdominal obesity was associated with chronic cough with an OR of 1.4 [1.2-1.7]. Interestingly, the authors ranked the risk factors according to the population attributable risk (PAR) calculated  $[f(OR-1)]/[1+f(OR-1)]$ , where  $f$  is the frequency of the risk factor and OR is the odds ratio for chronic cough in the population. Using this formula, abdominal obesity was defined as the 3<sup>rd</sup> risk factor in chronic cough, ranking higher than asthma, gastroesophageal reflux disease (GERD) or upper airway cough syndrome. When the results were stratified according to smoking status, abdominal obesity remains in the top ranking in former and current smokers according to PAR. However, in non-smokers, abdominal obesity is only the 7<sup>th</sup> risk factor and the association with chronic cough is not significant (OR 1.3 [0.95-1.7]). Further studies are warranted to establish whether obesity plays a significant role in the development of chronic cough and whether comorbid conditions increase the prevalence of chronic cough in obese subjects.

#### Specificity of the clinical approach towards chronic cough in obese patients

As explained above, obesity is a very common disease worldwide but its prevalence in patients with chronic cough has been inadequately studied. In the epidemiological study carried out in the UK in 2006, 20% of patients with chronic cough were obese [14]. This means that the proportion of obese patients with chronic cough is probably high in clinical practice. Should we manage chronic cough in obese patients differently from non-obese patients? The guidelines on chronic cough management may be applied in obese patients

albeit with some specific features. The algorithm of chronic cough management in obese patients is outlined in Figure 1. Asthma, one of the main causes of chronic cough, presents differently in obese patients. In the cluster analysis conducted by Haldar *et al.*, the authors found an obese asthma phenotype with non-eosinophilic inflammation [18]. The inflammatory profile of asthma may be different in obese patients compared to non-obese patients and the role of eosinophils in inflammation may be less crucial in obese asthmatics than non-obese asthmatics. However, sub-mucosal eosinophilic inflammation has also been found in asthma patients with obesity, which indicates that the association is probably more complex [19]. The obese-asthma phenotype is not a single entity and sub-phenotypes have been described depending on age, gender and asthma onset [20]. This probably involves various mechanisms of inflammation related to different endotypes. It is important to note that inhaled treatments appear to be less effective in obese patients with asthma. Indeed, there is evidence to show that inhaled corticosteroids and long-acting beta agonists are not as effective in asthma control in obese patients compared to non-obese patients [21, 22]. The real efficacy of inhaled therapies on cough has not been assessed in obese patients.

Cross-sectional epidemiological studies have demonstrated a higher prevalence of GERD in obese individuals compared to non-obese subjects. In a study involving 10,545 women, an increased risk of GERD was observed in obese patients with ORs of 2.92 (95% CI 2.35–3.62) with a BMI of 30–34.9 kg/m<sup>2</sup>, 2.93 (95% CI 2.24–3.85) with a BMI  $\geq$ 35 kg/m<sup>2</sup> compared to women with a BMI of 20–22.49 kg/m<sup>2</sup> [23]. Long-term complications of GERD such as erosive oesophagitis (EE), Barrett's oesophagus (BE), and oesophageal adenocarcinoma have been linked with obesity [24, 25]. However, obesity does not seem to affect treatment outcomes with proton pump inhibitors (PPI). In patients with GERD, a high BMI was associated with more severe EE at baseline. However, during PPI treatment, BMI was not a significant independent predictor of heartburn resolution or EE healing [26]. When obese

patients are treated with PPI therapy for reflux, no increased risk of BE or oesophageal carcinoma has been observed [27]. If a GERD-induced cough is suspected in clinical practice, PPIs should be tested [6]. PPIs are likely to have a similar effect on chronic cough in obese and non-obese patients. Robust evidence is needed to validate the use of PPIs in obese patients with GERD-induced cough.

A comprehensive history and physical examination are crucial in patients with chronic cough to rule out any life-threatening conditions and direct the investigation. In obese patients, clinicians should collect information relating to dietary habits, physical activity, eating patterns and the possibility of an eating disorder (binge eating disorder, night eating syndrome, bulimia), health consequences of obesity, patient expectations and motivation for change and previous treatments for obesity, according to the guidelines on the management of obese patients [28]. In addition to weight and height, waist and hip circumference should be measured especially during the follow-up. Indeed, waist and hip circumference is a better marker of adiposity especially visceral adiposity than BMI and it has been shown that waist circumference is significantly associated with hypertension, type 2 diabetes and OSAS [29]. Blood pressure should be routinely recorded in obese patients. Clinicians should be aware of obesity-related diseases such as diabetes, dyslipidaemia, cardiovascular, respiratory and joint diseases, and sleep disorders. As described below, some obesity-related diseases have an impact on chronic cough.

Minimal investigations in chronic cough should be carried out in order to determine the causes involved in cough. Fraction exhaled nitric oxide (FENO) is a helpful easy-to-use tool in patients with chronic cough because a high level of FENO is associated with cough variant asthma (CVA) and may predict the response to inhaled corticosteroids [30]. Obese individuals have a slight but significant increase in FENO compared to underweight individuals and obesity should be taken into account when FENO is performed in a context of chronic cough



[31].

### Chronic cough and OSA

It is a well-established fact that obesity is a risk factor for the development and progression of obstructive sleep apnoeas (OSA) [32]. The prevalence of OSA in obese patients is nearly twice that of normal-weight adults [33]. An association between chronic cough and OSA was initially proposed in 2007 [34]. Birring *et al.* reported 4 patients presenting with an isolated chronic cough who were subsequently found to have obstructive sleep apnoea. Cough improved rapidly with nocturnal continuous positive airway pressure (CPAP) therapy. In a retrospective study carried out in 75 patients with chronic cough associated with normal lung function test and chest X ray, the proportion of patients with sleep disorder breathing was as high as 44% [35]. Amongst them, 42% had severe OSA defined by an index of hypopnea and apnoea (IHA)  $\geq 30/h$ . Interestingly, GERD was found in 52% of patients with sleep disorder breathing. Ninety-three percent of the patients who underwent procedures to optimise sleep-disrupted breathing witnessed an improvement in their cough. In a prospective study carried out in 53 patients referred for the evaluation of a sleep-breathing disorder and having OSA, chronic cough was observed in 33% of patients [36]. Compared to patients without chronic cough, those with chronic cough were mostly females and nocturnal heartburn, dysphagia, chest pain and rhinitis were more common. In another study, chronic cough was observed in 39.4% of patients with OSA and only 12.5% of patients without OSA suggesting chronic cough is particularly associated with OSA [37]. Mean BMI was statistically higher in patients with OSA highlighting the importance of obesity in the development of OSA. In the multivariate analysis, GERD was statistically associated with chronic cough in patients with OSA with an OR of 10.4.

The mechanisms potentially responsible for the association of chronic cough with OSA have

not been yet elucidated. As described previously, GERD is consistently found in studies that have focused on OSA and chronic cough. Therefore, GERD is put forward by many authors as the primary mechanism for the development of cough in OSA. Intra-thoracic and intra-abdominal pressure changes during apnoea have been associated with the origin of GERD in OSA, but the mechanisms are probably more complex because GERD may interrupt sleep [38]. Upper and lower airway inflammation is observed in OSA and may also contribute to chronic cough [39, 40]. Trauma to the upper airways during each episode of apnoea-hypopnoea could also contribute to the development of cough [41]. According to some authors, oedema and inflammation of the soft palate, uvula and supra-laryngeal soft tissues observed during OSA may predispose patients to increased sensitivity to coughing and especially to the "tickling" sensation often experienced by patients with chronic cough [42].

CPAP therapy is classically used in OSA to improve IHA and may be effective in the treatment of cough in OSA patients. In a prospective study, 28 patients with chronic cough were enrolled to assess the effect of CPAP therapy on cough [43]. In this study, the STOP-BANG questionnaire was used to select the patients with a high probability of OSA. This questionnaire, based on symptoms and anatomical characteristics, predicts OSA with an intermediate risk if score is  $\geq 3$ . Twenty-two patients had a STOP-BANG score  $\geq 3$ , and among the 19 patients who accepted polysomnography and received CPAP treatment 7 had severe OSA. Leicester cough questionnaire (LCQ) score significantly improved after CPAP treatment. CPAP therapy seems to be of interest and may tackle cough hypersensitivity as suggested in a case report [44]. Indeed, cough reflex, measured by the citric acid test, improved after CPAP treatment and deteriorated after CPAP withdrawal. Moreover, in this case report, airway pH improves after CPAP therapy, which once again suggests the involvement of GERD in the association of chronic cough and OSA. Randomised controlled trials are needed in order to establish the real effect of CPAP treatment on chronic cough in

OSA patients.

### Chronic cough and diabetes

Obesity is a recognised risk factor of type 2 diabetes mellitus [45]. In a study carried out in 33,939 men, obesity was associated with type 2 diabetes with an OR of 3.88 [95% CI 1.94–7.77] [46]. Recently, it has been suggested that type 2 diabetes may be a risk factor of chronic cough. Indeed, in a cross-sectional study, self-reported chronic cough/phlegm was more common in diabetic patients compared to the general population but only in patients 45-64 years old [47]. Indeed, in those patients, chronic cough/phlegm was reported by 27.6% of diabetic patients and 16.7% of the general population. No difference was observed between each group after 65 years of age. The prevalence of chronic cough increases in the general population after 65 years of age and the same prevalence was observed between both groups. Other causes of cough (GERD, COPD, Drugs, other respiratory diseases...) may appear with age and could explain why no difference was observed between diabetics and non-diabetics after 65 years of age. Further studies are needed to confirm the link between cough and diabetes.

Interestingly, it has been described that gliptin, a dipeptidyl peptidase-4 inhibitor used in diabetes mellitus, is involved in drug-induced cough [48-50]. The prevalence of cough was 1.7% vs. 1.0% in the placebo arm of a randomised controlled study [48]. The mechanism seems to be similar to that observed with angiotensin converting-enzyme inhibitors [49].

### Weight loss and chronic cough

Given the fact that inhaled corticosteroids are less effective in obese patients with asthma, weight loss has been suggested as an option in obese patients with asthma [51]. The combination of dietary intervention and exercise has been shown to improve asthma control in

obese patients [52]. Despite a lack of evidence, diet and exercise intervention may be considered in obese patients with chronic cough associated with asthma. A significant improvement in the ACQ (Asthma Control Questionnaire) score has also been observed with bariatric surgery in obese patients with asthma and this procedure may be interesting in obese asthmatics [53]. In obese patients with cough variant asthma, no data are available to support the beneficial effect of bariatric surgery on chronic cough.

Weight loss procedures are also linked to an improvement in GERD-related symptoms. In a cross-sectional survey performed on 44,997 patients between 2006 and 2009, weight loss was associated with fewer symptoms in a dose-dependent manner [54]. A structured weight loss program is needed to significantly reduce GERD symptoms. Indeed, in a prospective cohort study carried out on overweight/obese subjects (BMI 25-39.9 kg/m<sup>2</sup>), a structured weight loss program was assessed. This included dietary changes, increased physical activity and behavioural changes. A significant decrease in the overall prevalence of GERD (15 vs. 37%) and the mean GERD symptom score (1.8 vs. 5.5) was observed in patients included in the treatment arm compared to patients in the control arm [55]. In patients with GERD-induced cough, the traditional dietary changes combined with weight reduction advice in the form of an Energy Prescription (EP) led to LCQ improvement compared to traditional dietary changes alone. Interestingly, a significant correlation between baseline high calorie and LCQ scores or fat intake and LCQ scores was observed. The role of diet or adipose tissue on chronic cough should be studied to enhance our knowledge of cough in obese patients.

## Conclusion

The link between obesity and chronic cough has been suggested in the literature. In the guidelines on chronic cough management, no difference has been highlighted between obese and normal-weight individuals. However, emergent causes of chronic cough such as OSA or

diabetes should be taken into account in clinical practice. The beneficial effect of weight loss has been demonstrated in many obesity-related diseases. Weight-loss procedures may constitute part of the treatment of chronic cough in obese patients but further studies are warranted to support the use of these interventions in chronic cough.

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Table 1: Management of chronic cough in obese patients. \* Family history, dietary habits, frequency and type of physical exercise, eating pattern and possible presence of an eating disorder (binge eating disorder, night eating syndrome, bulimia), presence of depression and other mood disorders, drugs, endocrine abnormalities, psychosocial factors, chronic stress, smoking cessation, previous treatments for obesity. \*\* diabetes, hypertension, dyslipidaemia, cardiovascular diseases, respiratory and joint diseases, sleep disorders. BMI: body mass index, GERD: gastro-oesophageal reflux, CPAP: continuous positive airway pressure, CT: computed tomography, FENO: Fraction exhaled nitric oxide, HRCT: high-resolution CT, ICS: inhaled corticosteroids, LABA: long acting beta agonist, LTRA: leukotriene antagonist, OSA: obstructive sleep apnoea, PPI: pump proton inhibitor.

Cough for at least 8 weeks and BMI $\geq 30$ k/m <sup>2</sup>
<p>a. Patient characteristics:</p> <ul style="list-style-type: none"> <li>- Life-threatening conditions <ul style="list-style-type: none"> <li>- Query: cough characteristics, history of obesity, etc.*...</li> <li>- Sleep apnoea questionnaire</li> <li>- Physical examination including waist-to-hip ratio, blood pressure, signs of obesity-related conditions**</li> <li>- Chest X-ray</li> </ul> </li> </ul>
<p>b. Consider the 4 most common causes of chronic cough and treat if present</p> <ul style="list-style-type: none"> <li>- GERD If clinically suspected, test with PPI and diet lifestyle change</li> <li>- Asthma Spirometry with reversibility <math>\pm</math> bronchial challenge test Allergy evaluation Treatment: ICS<math>\pm</math>LABA, LTRA, trigger avoidance, weight loss</li> <li>- Upper Airways Cough Syndrome Sinus imaging, nasofibroscopy, allergy evaluation Treatment: antihistamine and/or nasal corticosteroids</li> <li>- Non-asthmatic Eosinophilic Bronchitis Sputum eosinophilia, FENO, allergy evaluation Treatment: ICS, trigger avoidance</li> </ul>
<p>c. Consider 2 emergent causes in obese patients</p> <ul style="list-style-type: none"> <li>- OSA Sleep questionnaire and, if positive, nocturnal polygraphy Treatment: CPAP treatment</li> <li>- Diabetes Blood glucose levels and, if abnormal, HbA1c Treatment: specific diabetic treatments</li> </ul>
d. Weight loss interventions if the patient is motivated
<p>e. Further investigations if cough proves refractory:</p> <ul style="list-style-type: none"> <li>- 24-hour oesophageal pH/Impedance monitoring</li> <li>- HRCT (high-resolution computed tomography), sinus CT scan</li> <li>- Swallowing evaluation</li> <li>- Bronchoscopy</li> <li>- Environmental assessment</li> </ul>