

## REVIEW

# Gastro-oesophageal reflux and bronchial asthma: current status and future directions

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In recent years there have been several reports suggesting an association between bronchial asthma and gastro-oesophageal reflux; however a cause and effect relationship has not been proven yet. Confirmation of such a relationship is likely to have far reaching implications on the management of asthma. Reliable assessment of this issue is hampered by the presence of various lacunae in most of the published studies. Hence it is essential to carefully examine the strength of data suggesting a link between asthma and reflux. This article critically analyses currently available literature on the subject (including published reviews, meta-analyses, and randomised clinical trials in the English language) and summarises valid conclusions that can be drawn; it also proposes a framework for future studies to resolve the issue.

## EVIDENCE SUGGESTING A LINK BETWEEN GOR AND BRONCHIAL ASTHMA

Broadly, there are two lines of scientific data suggesting a connection between GOR and asthma. "Prevalence studies" include epidemiological data showing higher prevalence of GOR among those with asthma compared to the general population and "treatment studies" refer to the demonstration of improvement in asthma control with medical or surgical treatment of GOR.

### Prevalence studies

This body of scientific data is derived from studies that have calculated the prevalence of GOR among patients with asthma. Before the advent of 24 hour oesophageal pH monitoring, which is the current gold standard for confirmation of GOR, barium swallow studies, oesophageal manometry, and radionuclide scintigraphy were some of the methods used for this purpose. These have now largely been replaced by continuous ambulatory oesophageal pH monitoring, based on which at least 50% of adults<sup>1–5</sup> and children<sup>6–8</sup> have evidence of GOR. Some studies in adults indicate that the prevalence may be even higher. Besides the actual demonstration of abnormal pH, there are some reports that have used less stringent indirect criteria for defining GOR including histological evidence of oesophagitis<sup>9</sup> and symptoms suggestive of GOR<sup>10</sup>; not surprisingly GOR "diagnosed" by these surrogate methods is far higher than that by pH diagnosis. The significantly higher prevalence of GOR in asthma compared to the general population has been taken to suggest that the two conditions may be causally linked.

There are other indicators suggesting a stronger link between GOR and bronchial asthma. For example, a study documenting proximal as well as distal oesophageal reflux among children with asthma showed that about three quarters of them had distal reflux and almost two thirds had proximal reflux.<sup>3</sup> Likewise reflux is reportedly more common among those with "difficult to control" asthma than well controlled patients,<sup>11</sup> suggesting that reflux may be contributory to poor control. Since reflux is believed to be more frequent at night and symptoms of asthma are often nocturnal, demonstration of correlation between night time GOR and cough in asthmatics lends further strength to a proposed linkage.<sup>3, 10</sup>

**Abbreviations:** FEV<sub>1</sub>, forced expiratory volume in the first second; GOR, gastro-oesophageal reflux; PEFR, peak expiratory flow rate

There has been considerable interest during the last two decades over the possibility of a link between gastro-oesophageal reflux (GOR) and bronchial asthma. This is evidenced by a vast body of scientific literature including randomised trials, anecdotal experiences and case reports, many of which suggest such a link. GOR is reported to be particularly prevalent among patients with asthma and many researchers suggest that it may be a predisposing factor for asthmatic episodes. Some have even postulated a causal relationship between the two conditions. However, others are more circumspect, believing that although the association is not purely by chance, the linkage may be more casual than causal. Clinical experience suggests that early diagnosis and treatment of GOR often leads to better control of asthma.

However, despite the presence of numerous studies, a cause and effect relationship between GOR and bronchial asthma has not been established and the controversy as to whether GOR causes bronchoconstriction or is simply a temporal association remains to be resolved. The objectives of this review are to critically review currently available data that suggest a link between GOR and bronchial asthma, to analyse the strength of the evidence pointing in this direction, and to define a framework for future studies and clinical trials on this subject.

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### Treatment studies

There are numerous clinical trials documenting the effects of GOR therapy on asthma control. They differ widely in quality and methodology and therefore in their results, interpretation, and conclusions. For convenience, these may be grouped together as (i) those that document improvement in symptoms of asthma, (ii) those that demonstrate improvement in objective measures of asthma severity, and (iii) those that show decrease in asthma medication with treatment of GOR.

In a cohort of difficult to control asthmatics, omeprazole and cisapride therapy for seven weeks resulted in complete improvement of symptoms in 86%, moderate improvement in 11%, and lack of improvement in only 4% patients. Symptoms reappeared rapidly following discontinuation of GOR therapy.<sup>12</sup> Likewise, ranitidine led to a decline in nocturnal asthma symptoms with a good degree of correlation between asthma symptoms and degree of acid reflux in children<sup>13</sup> and adults.<sup>14</sup> In general H<sub>2</sub> receptor antagonists have been beneficial in about 50% of treated patients.<sup>13–17</sup> A group of researchers identified 12 studies over a 30 year period (1966–96) assessing the effect of medical antireflux therapy on asthma control and found that almost 70% of over 300 subjects had an improvement in asthma symptoms.<sup>18</sup> Symptomatic improvement has been documented with antacids and lifestyle changes,<sup>19</sup> though this effect has not been consistent. Most studies with cisapride have shown beneficial effects in at least half the patients treated.<sup>20–21</sup> As per a systematic review comprising eight comparative studies, surgical procedures to prevent reflux are reported to be even more efficacious than medical therapy.<sup>22</sup> Surgery may be beneficial even in patients who fail to respond to medical therapy.<sup>23–24</sup>

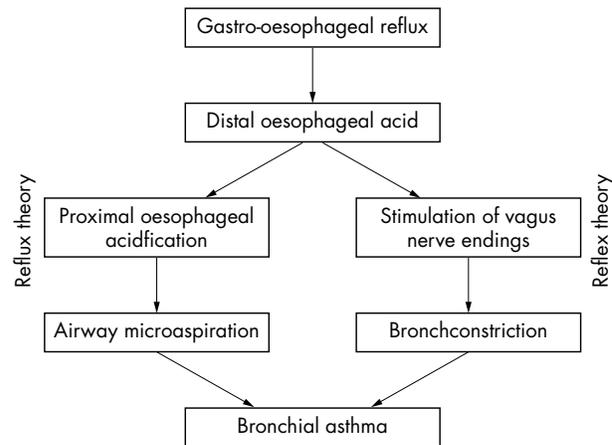
Although fewer in number, some studies have documented improvement in objective parameters of pulmonary function with treatment of GOR. Studies in adults have shown improvement in peak expiratory flow rate (PEFR)—both morning and evening measurements—and forced expiratory volume in the first second (FEV<sub>1</sub>),<sup>14–18–25</sup> although the proportion of patients showing this improvement has ranged from a minority<sup>18</sup> to as many as 75%.<sup>14</sup> There are also reports of improvement in quality of life and symptom scores with abolition of reflux.<sup>25</sup>

Most short term studies have shown that there is improvement in symptoms and pulmonary function during and after medical treatment or surgical correction for GOR. However, a long follow up study showed that the results of medical therapy were inferior to surgical treatment particularly when therapy for GOR was discontinued.<sup>26</sup>

Some studies have focused on reduced requirement of asthma medication by concomitant treatment of GOR. About two thirds of wheezing infants with GOR could decrease use of flunisolide compared with none among those who did not have GOR; the authors suggested that control of GOR improves morbidity and need for asthma therapy.<sup>27</sup>

### MECHANISMS OF A POSSIBLE RELATIONSHIP BETWEEN GOR AND BRONCHIAL ASTHMA

Figure 1 summarises the current concept of theories that explain a link between asthma and GOR. The reflux theory suggests that symptoms of asthma are due to reflux of acid into the oesophagus followed by aspiration into the proximal airway.<sup>10</sup> Animal studies have proven that once the trachea is acidified, there is demonstrable increase in airway resistance. The data in support of this hypothesis include scintigraphic demonstration of aspiration of radiolabelled isotope into the airway in some patients with GOR and respiratory symptoms.<sup>28</sup> Others have been able to show tracheal acidification occurring in concert with oesophageal reflux.<sup>29–30</sup>



**Figure 1** Mechanisms of a linkage between asthma and GOR.

The reflex theory suggests that distal oesophageal acidification results in vagal stimulation and consequent bronchoconstriction, independent of airway microaspiration.<sup>31–32</sup> This theory gains support from the observation that not all patients who develop bronchospasm have demonstrable proximal oesophageal acidification. Further, even among those who show abnormal proximal oesophageal pH, there is improvement in respiratory symptoms with control of distal GOR alone. Some workers using dual probes in the upper oesophagus and trachea have found that changes in proximal oesophageal pH did not correlate with changes in PEFR.<sup>33</sup> Lastly, in experimental animals, increase in airway resistance was abolished by bilateral cervical vagotomy.<sup>34</sup>

It is significant to note that both theories suggest that GOR is the primary pathology and asthma is secondary. To this extent, both theories are not different from each other. However, neither can explain why all patients with distal oesophageal acidification do not manifest airway constriction. Thus while these theories provide some idea of the cause of respiratory symptoms in GOR, they do not establish a causal link between GOR and asthma.

It is also possible that physiological changes in asthma including increased lower oesophageal pressure, the mechanical influence of a depressed diaphragm caused by hyperinflation, and cough mediated increased abdominal pressure may contribute to GOR to some degree. In addition, some of the medications used for treatment can aggravate GOR<sup>35</sup>; thus there is a perception that GOR may be an effect rather than cause of chronic respiratory conditions. However, some workers have shown that inhaled medication has negligible adverse effect on oesophageal tone.<sup>36</sup>

### EVIDENCE AGAINST A LINK BETWEEN GOR AND BRONCHIAL ASTHMA

Although GOR is demonstrable in a large majority of patients with asthma, particularly those with severe disease, the reverse does not seem to be true and asthma is not more prevalent among individuals with GOR compared to the normal population. Reflex mediated cough and upper airway symptoms are no doubt very common, however reversible airway obstruction does not appear to be more common.

Secondly, the association of GOR with respiratory conditions is non-specific as it is observed in a wide variety of other airway disorders. Some upper airway conditions associated with GOR include chronic cough,<sup>37</sup> wheezing,<sup>27</sup> stridor,<sup>38</sup> recurrent croup,<sup>35</sup> sinusitis,<sup>39</sup> laryngomalacia, and subglottic stenosis.<sup>9</sup> From studies that have reported the prevalence of GOR among lower respiratory conditions, it is clear that there

is an association not only with asthma, but also with recurrent pneumonia,<sup>40</sup> bronchitis,<sup>41</sup> cystic fibrosis,<sup>42–43</sup> chronic obstructive lung disease,<sup>44</sup> and after lung transplant.<sup>45</sup> Further, studies that have evaluated GOR among various respiratory conditions have shown that the prevalence is comparable in asthma, chronic cough,<sup>46–47</sup> recurrent pneumonia,<sup>48</sup> and cystic fibrosis.<sup>49</sup> The suggested link is further weakened by the observation that GOR, when associated with cough or asthma, does not cause or aggravate existing airway inflammation measured by induced sputum cell counts, fibrinogen level, and exhaled nitric oxide.<sup>51</sup>

Another strong criticism against a linkage between asthma and GOR is that most studies demonstrating improvement in asthma symptoms or objective parameters of lung function have shown this effect in only a minority of treated patients, with no explanation for failure to observe the effect in the remainder.<sup>1–18–51</sup> Likewise although there is some beneficial effect on asthma symptoms with use of omeprazole, this was reported to be no different with the use of placebo.<sup>52</sup> Other authors have reported that GOR therapy does not result in any improvement in specific objective measures of airway hyper-reactivity such as provocative concentration to decrease FEV<sub>1</sub> by 20% (PC20), PEFR variability, and asthma symptom scores.<sup>51–53–55</sup> A group of researchers working with patients believed to have recalcitrant asthma related to GOR found that only a small minority of patients demonstrated temporal correlation between the occurrence of a reflux episode and bronchospasm; the two events were unrelated in the majority.<sup>56–57</sup> A systematic review published in 2001 evaluated all forms of GOR therapy and concluded that there is no evidence to recommend treatment of reflux in asthma, but emphasised the need for larger trials with longer duration of treatment.<sup>58</sup> The updated Cochrane database systematic review published in 2003 showed that in asthmatics with GOR, antireflux therapy did not consistently improve pulmonary functions, asthma symptoms, nocturnal asthma, or result in any decrease in the use of asthma medication.<sup>59</sup> The review incorporated 12 clinical trials including six that used proton pump inhibitors, five that used H<sub>2</sub> receptor antagonists, and one that evaluated patients after surgery. The review concluded that some subgroups of patients with bronchial asthma may benefit from GOR therapy, but it is not possible to predict this from currently available data. However, analysis of the trials included shows that asthma was diagnosed based on symptoms, partially or completely in four of them, GOR was diagnosed based on symptoms in some or all patients in four studies, and one trial also included patients with chronic obstructive pulmonary disease.

Some studies in more recent years have been able to demonstrate a limited degree of improvement in pulmonary functions, but not a decrease in use of asthma medication,<sup>60</sup> suggesting that even objective changes did not correlate with asthma control.

### PITFALLS IN CURRENTLY AVAILABLE DATA

The majority of studies suggesting a link between bronchial asthma and GOR suffer from one or more of the following lacunae (see box 1), making it difficult to interpret their findings and generalise the conclusions drawn.

#### Imprecise definitions

Many trials have used rather loose definitions of “bronchial asthma” for inclusion of patients. In some cases, only history suggestive of asthma has been taken as an eligibility criterion. Among the few studies that have used objective criteria to define asthma, most have neither demonstrated airway hyper-responsiveness nor reversibility of bronchoconstriction. In some studies, children with recurrent respiratory

### Box 1: Lacunae in currently available data

#### Imprecise definition of bronchial asthma

- Symptoms loosely labelled as asthma.
- Lack of objective measurement.
- Failure to demonstrate airway hyper-reactivity.
- Failure to demonstrate reversibility of bronchoconstriction.

#### Imprecise definition of GOR

- Suggestive symptoms labelled as GOR.
- Poorly sensitive and specific tests of GOR used for definition.
- Lack of objective measurements to assess severity of “GOR”.

#### Flaws in study design

- Inadequately powered (due to inappropriate sample size) to confirm conclusions drawn.
- Lack of controls to compare effects reported.
- Failure to use placebo to compare effects.
- Few studies have been designed as randomised trials.
- Lack of measurement of objective parameters of asthma or GOR.
- No long term effects studied.

#### Flaws in interpretation

- Observations in a minority extrapolated to entire study group.

symptoms have been labelled as having asthma; therefore it is not clear whether they had asthma or another condition. Interestingly, in some of these studies, a family history of asthma is absent in all the cases of GOR related reactive airway disease. Thus, from the definitions used, it is sometimes difficult to be sure that the enrolled patients were really suffering from bronchial asthma. It is likely that respiratory symptoms are secondary to reflux, rather than asthma. This view is strengthened by the observation that even patients with chronic obstructive pulmonary disease—wherein airway obstruction is irreversible—have high prevalence of reflux.

Another major pitfall is the absence of precise definitions and standards of measurement of reflux; some studies include only symptoms suggestive of reflux. In the absence of objective proof of GOR with a 24 hour pH study, surrogate markers such as symptoms of reflux, oesophagitis, etc are poor substitutes. Interestingly, GOR detected in a large majority of those with airway disease is clinically silent; whereas GOR otherwise usually leads to symptoms. The reason for this discrepancy is also not clear.

#### Flaws in study design and methodology

To summarise this aspect, many studies have been conducted with an inappropriate sample size,<sup>25–51–53–56</sup> hence are inadequately powered to confirm the conclusions drawn. The lack of controls, failure to use placebo, and lack of objective outcome measures vitiates the quality of some studies. A major lacuna is that there is almost no well designed study that has evaluated patients with a long term follow up.

#### Flaws in interpretation of results

Many studies have demonstrated beneficial effect of reflux therapy in a minority of recruited persons,<sup>23–30–49–56</sup> but some have attempted to extrapolate the results to the entire

### Box 2: Conclusions that can be drawn from currently available data

- There is a higher prevalence of GOR among patients with asthma, than in the general population.
- Treatment of GOR improves reflux symptoms and some of the respiratory symptoms, but fails to result in objective improvement of asthma or decrease in asthma medication in the majority of treated patients.
- There may be a subset of asthmatics, possibly those with more severe disease or more severe GOR who may benefit with antireflux therapy, but this group has not been identified conclusively yet.
- There is no proven “cause and effect” relationship between asthma and GOR as yet.

asthmatic population. In this regard, it must be highlighted that none of the studies have calculated relative risk or performed a “numbers needed to treat” analysis. In several studies measuring multiple parameters, there is improvement in one or other outcome parameter, but no change in others. The usual pattern is detection of improvement in symptoms or asthma score, but failure to document improvement in pulmonary function tests or airway hyper-reactivity.<sup>15–25</sup> This suggests that the observed effects may not be consistent. It is also possible that the benefit observed is due to better adherence to asthma medication that occurs with closer monitoring and follow up during a clinical trial than the effect of GOR therapy.

### CONCLUSIONS THAT CAN BE DRAWN FROM CURRENTLY AVAILABLE DATA

Box 2 summarises valid conclusions that can be drawn from currently available data.

### GUIDELINES FOR FUTURE STUDIES

Owing to the imprecise nature of current knowledge linking GOR and bronchial asthma, and the pitfalls in interpretation of currently available data, we propose that the following guidelines be followed in studies being undertaken in the future. These have been summarised in box 3.

#### (1) Use of precise definitions

*For asthma*—Subjects recruited should have demonstrable reversibility of airway constriction or PEFr variability or objective pulmonary function parameters of asthma or documented airway hyper-responsiveness, before being labelled as having asthma.

*For GOR*—GOR must be diagnosed by a 24 hour pH study, preferably with documentation of reflux index, number of reflux episodes, percentage of time pH <4.0 during sleep, and correlation of pH changes with episodes of cough and exacerbation of asthma. The quality of pH study may be improved by simultaneous measurement of proximal and distal pH using dual probes and the measurement of PEFr and FEV<sub>1</sub> during or immediately after a reflux episode.

#### (2) Appropriate study design

Future trials must not be undertaken in the absence of an appropriate sample size. They must be necessarily double blinded, placebo controlled randomised trials, preferably incorporating a crossover design.

#### (3) Outcome measures

These must be precise and always include one or more objective measurements in addition to changes in subjective

### Box 3: Guidelines for future studies on asthma and GOR

#### Precise definition of bronchial asthma

- Demonstrate airway reactivity.
- Demonstrate reversibility of airway constriction.
- Use objective measures of pulmonary function for follow up.

#### Precise definition of GOR

- 24 hour oesophageal pH study using single or dual probes.
- Calculate reflux index or other objective measures to assess severity of reflux.

#### Appropriate study design

- Calculate sample size.
- Design a placebo controlled randomised trial.
- Preferably incorporate a crossover design.

#### Precise outcome measures

- Use objective parameters to assess changes in status of asthma and GOR.
- Use multiple parameters to study change in asthma status including symptom score, pulmonary function, and change in medication.

#### Long term follow up

- Follow up should ideally include serial monitoring of asthma control parameters and reflux; preferably these should be documented after discontinuation of reflux therapy also.

aspects. It will be useful to measure GOR serially in patients during follow up and correlate changes with alterations in objective pulmonary measurements.

#### (4) Follow up

Future studies must be designed with a long term follow up including monitoring after discontinuation of reflux therapy, so that the effects of antireflux and antiasthma therapy on asthma control and GOR can be studied.

### CONCLUSION

Although there is no dearth in the quantity of scientific literature suggesting a possible connection between asthma and GOR, the quality of many studies and the results and conclusions drawn need to be interpreted with caution. Currently, there is no evidence that treatment of GOR consistently improves outcome in bronchial asthma. Future trials need to be properly designed to address these issues.

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