Mini Review

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Asthma and COVID-19: Asthma as Risk Factor for COVID-19 Infection?

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Abstract

Background: Asthma is an inflammatory pulmonary disease. Cellular immune responses are the most frequent immunological response in asthma. Concerns about risk factors for infection have increased with the COVID-19 pandemic. Primary studies indicated that children with accompanying comorbidities such as asthma might be at greater risk of COVID-19 comparable to adults with similar comorbidities.

Methods: This review study aimed to investigate the association between asthma COVID-19 infection. Google scholar database on October 1st, 2020 was used to identify eligible articles. The Keywords used to find papers: (Asthma*) and (COVID-19*), (Asthma*), and (COVID-19*) and (risk factor*). The publication time was limited to 2020 onward. A total of 6780 papers were identified by the initial search. Two reviewers independently reviewed the abstracts and full-texts. Reports on the topic of asthma as a risk factor for COVID-19 infection were included in this review.

Results: 29 studies were included in this review. Given that overexpression of ACE2 in rhinovirus infections, and activation of ACE2 regulates many antiviral responses to cytokines. This may lead to cytokines exacerbation which is the COVID-19 pathological response. These results suggest that viral infections that cause worsening of asthma show synergistic biomolecular interactions due to COVID infection. Besides, people with asthma have a delay or deficiency in the antiviral immune response, with deficiency and delay in lung cell interferon (IFN)-α,5 IFN-β6, and IFN-λ7 responses reported in many studies, and deficiency of the latter IFN clearly related to increased asthma exacerbation.

Conclusion: Clinical studies in different countries showed that asthmatic patients with COVID-19 infection are a small fraction of all infected patients. Although patients with asthma are vulnerable to respiratory infections such as rhinoviruses, there is no conclusive evidence to support an association between asthma and COVID-19 infection. Various studies suggested that asthmatic patients continue medications particularly inhaled corticosteroids and avoid allergens.

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Asthma is a lifelong pulmonary inflammatory disease of the airways [1]. Symptoms include episodes of wheezing, coughing, chest tightness, and shortness of breath [2]. Asthma is now considered an umbrella diagnosis for several diseases with distinct mechanistic pathways (endotypes) with variable clinical phenotypes (childhood atopic, non-atopic, middle-aged obese, and

elderly late-onset). An important molecular mechanism of asthma is the chronic inflammation of conducting airways, even during asymptomatic periods [3]. This inflammation is different in various asthma endotypes and may broadly be divided into Th2 high (atopic, eosinophilic) and Th2 low (non-atopic, non-eosinophilic) endotypes [4]. Cellular immune responses are the most frequent immunological response in term of pathogenesis of asthma. Type 1 and type 2 immune responses are regulated by both T helper cells (1 and 2), respectively. Th1 cells secrete IL-2 and IFN-γ and stimulate type 1 immunity characterized by phagocytic and anti-viral activity [5]. T helper 2 cells mainly secrete inflammatory cytokines such as IL-4, IL-5, and IL-13 that stimulate T helper 2 type immunity characterized by eosinophilia and high antibody titers. Although, T helper 2 type immune response is induced by parasites, it is also associated with the atopic disease; allergy, allergic rhinitis, and asthma [6]. T helper 2 type responses are mediated by eosinophils, basophils, mast, Th2, and IgE-producing B cells. Increased production of type 2 cytokines leads to allergen-triggered IgE hypersensitivity and activation of mast cells, basophils, eosinophils, airways epithelial cells, and remodeling of airways.

There are several evidences regarding asthma as risk factor for asthma and viral infections [7-10]. Some studies evident that some viruses such as Respiratory Syncytial Virus (RSV), influenza viruses, and human rhinoviruses are highly corelated with asthma exacerbations. Despite the rarity of coronaviruses, parainfluenza viruses, adenoviruses, and the more recently identified metapneumoviruses and bocaviruses, they are also involved [10]. ACE2 is the SARS-Co-V2 receptor, which has recently been identified as an interferon-stimulated expression gene. Zieger et al. Stated that stimulation of primary epithelial nasal cells with interferon increased ACE2 expression. Because ACE2 is part of interferon stimulated genes (ISGs) [11]. Rhinovirus infections affect the overexpression of ACE2. Activation of ACE2 regulates many antiviral responses to cytokines. These results suggest that viral infections that cause worsening of asthma show synergistic bio molecular interactions due to COVID infection. Human Rhinovirus (HRV) and coronavirus (HCoV) infections are associated with both upper respiratory tract illness (the common cold) and lower respiratory tract illness (pneumonia) [12]. Although coronaviruses were detected as agents of respiratory infections approximately 40 years ago [13,14], in common with COVID-19 outbreak, since both of them are a type of respiratory disease, many asthmatic patients are worry about their health condition. On the other hand, because underlying diseases can increase the risk of COVID-19 disease and mortality, concerns have been raised.

In May 24, 2020, the US Centers for Disease Control and Prevention (CDC) have proposed that "moderate to severe asthmatic patients may be at higher risk of getting very ill from COVID-19 [15]. Some research, stated that data mostly on critically ill patients, there does not appear to be an elevated prevalence of asthma [16,17]. The results of a review proposed that asthma seems to not be a risk factor for COVID-19, however patients who recently used corticosteroids may be at a higher risk of severe COVID-19 [18]. According to the IPCRG , patients are still struggling to differentiate their symptoms between asthma flare-ups and COVID-19. They may therefore delay seeking care for asthma or COVID-19. Interestingly, clarity does not appear to have improved as the weeks have passed. People have recurrences or waves of repeated symptoms, and it is difficult to understand whether the symptoms are related to an asthma exacerbation or to COVID-19 [16]. According the variety of evidences about asthma and COVID-19, it seems that there need more investigations to reach out the relationship between asthma as risk factor of COVID-19. The question of this research is that, based on the current evidences, is it possible to consider asthma as a risk factor of COVID-19?

Methods and Materials

The literature search using the following search strategy was conducted on Google scholar database on October1th, 2020 to identify eligible articles: (Asthma*) and (COVID-19*), (Asthma*) and (COVID-19*) and (risk factor*). The publication time was limited to 2020 onward. A total of 6780 papers were identified by the initial search. Two reviewers independently reviewed the abstracts and full-texts. Reports on the topic of asthma as risk factor for COVID-19 infection were included in this review.

Results

Overall, 29 studies regarding asthma and COVID-19 patients were included in the final analysis. Various studies have been performed on the effects of asthma as a risk factor for COVID-19. People with asthma have been shown to be exposed to the dangerous and sometimes fatal consequences of respiratory viruses such as the common cold compared to non-asthmatic people, and lack of control or poor control of asthma can lead to a poor prognosis for worsening respiratory infections in people with asthma [19]. Clearly, people with asthma have a delayed or deficiency in the antiviral immune response, with deficiency and delay in lung cell interferon (IFN)-α,5 IFN-β6 and IFN-λ7 responses reported in many studies, and deficiency of the latter IFN clearly related to increased asthma exacerbation severity [20-22]. These results may indicate that asthma is a potential risk factor for COVID-19 infection [46]. In July 2020 a study in Philadelphia concluded that exposure to a respiratory virus (especially RV) can exacerbate asthma symptoms and exacerbate and recur asthma episodes in children and adults. People with asthma are thought to be at higher risk for COVID-19 [23]. In a study, nasal airway analysis in two groups of healthy people with asthma showed that the genes involved in COVID-19 infection, in particular ACE2 and TMPRSS2, are affected by inflammation of cytokines and interferon, and as a result, type 1 specific responses that are exacerbated in patients with asthma can increase sensitivity to COVID-19 [24]. In confirmation of the

results of this study, a study conducted by Yoon Seok Chang in China in 2020 found that the prevalence of asthma and allergic diseases in patients with COVID-19 is still lower than expected, which is a possible hypothesis: 1- Decreased ACE2 enzyme expression. 2 - Decreased expression of TMPRSS2, which divides the virus protein into two subunits to enter the cell in the form of membrane fusion. 4 - Potential beneficial effect by therapeutic agents such as inhaled corticosteroids [25].

A study conducted in the United Kingdom 2020 (by Pennington) on the relationship between the risk of developing COVID-19 in hospitalized patients was significantly lower than the prevalence of asthma in patients hospitalized with influenza compared to those who were not hospitalized. Having asthma cannot be an independent risk factor for intubation in hospitalized patients even after adjusting for BMI and age [26]. Although there is not enough evidence to prove that asthma is a risk factor for COVID-19, it is believed that all children and adolescents should remain on their asthma control program during the COVID-19 pandemic [27].

The results of a study by Schultze in the United Kingdom showed that people with COPD and asthma who were given inhaled corticosteroids had a higher risk of dying from COVID19 (compared with those who were short-acting β agonist was prescribed) [28]. A study by Raju, et al. in India looked at whether ICS treatment may affect COVID-19-related mortality, and concluded that long-term treatment with ICS suppressed the immune system and the risk of developing COVID-19 increases. W.H.O does not recommend treatment with ICS , but discontinuation of ICS in patients with severe asthma or COPD puts patients at risk for severe exacerbations, so there is insufficient evidence to rule out ICS treatment in asthma [29]. Application of anti-IgE antibody omalizumab could reduce the severity of asthma, and evidence showed that people with asthmatic asthma had a lower risk of developing severe alveolar disorders. In fact, asthma or the omalizumab antibody or both may have a protective effect [30].

Discussion and Conclusion

Primary clinical studies indicate that children with accompanying comorbidities such as asthma may be at greater risk of COVID-19 comparable to adults with similar comorbidities [31]. In a study conducted by Kumar, et al in 2020, it was hypothesized that asthma was one of the most common underlying diseases in patients with COVID-19, but there was no evidence that asthma medications, such as bronchodilators or corticosteroids, and histamine can increase the risk of COVID-19. As a result, children with asthma should continue maintenance therapy at the same dose, but spirometry and PEFR should be avoided because of the risk of transmitting the virus [32]. People with asthma have more severe clinical manifestations of common viral infections than people without asthma, which is also associated with increased asthma control. In this way, if the asthma is not well controlled, the viral infection will worsen the condition. Intrinsic antiviral immune responses are inadequate and delayed in most patients with asthma. For example, interferon is not produced in these people as needed, so in the presence of the virus there may be an exacerbation of asthma symptoms [33].

Viruses usually provoke asthma exacerbations. COVID-19, like other viruses, causes asthma exacerbations, which is why asthma is considered a risk factor for severe COVID-19. Given that most common symptoms of COVID-19, dry cough and shortness of breath, are similar to the exacerbated and acute symptoms of asthma, it is difficult to differentiate between the clinical symptoms of COVID-19 and worsening asthma. Fever is a common symptom among COVID-19 patients, however there is no asthmatic condition in which asthma is triggered by an infection. For anyone with aggravated pulmonary symptoms, such as people with asthma, COVID-19 screening protocols should be used. Appropriate asthma control helps prevent the exacerbation of asthma in COVID-19. It is recommended that people with asthma continue to take their medications during a pandemic. Observe other factors such as avoiding allergens, hand hygiene and social distance [34].

In critical care, asthma prolonged intubation in patients with severe respiratory symptoms and requiring intubation; especially in younger patients (> 65 years). These data suggest that younger people with asthma may need more attention because they have a persistent lung defect in the presence of COVID-19, which leads to a longer intubation period (Mean 10.17 ± 6.9 days in patients with asthma and 5.9±5.28 days in patients without asthma).Also, the length of hospital stay in the 50-64 age group was longer among those with a history of asthma than in those without asthma, but this was not the case in the younger and older age groups. However, asthma in patients with COVID-19 it was not associated with an increase in mortality and was not associated with an increase in acute respiratory distress syndrome [35]. Chhiba, et al confirmed that, hospitalization and mortality rates were not significantly different between COVID-19 patients with and without asthma. In this study, the mortality rate in COVID-19 patients with asthma (3.6%) and COVID-19 patients without asthma (4.9%) was not significantly different. However, the rates of obesity, HTN , COPD , CAD , OSA and GERD were significantly increased in patients with COVID-19 positive asthma. The prevalence of allergic rhinitis, rhinosinusitis, and immune system dysfunction was also increased in COVID-19 patients with asthma [36].

Some studies indicated a lack of association between asthma and COVID-19. A survey showed, China [28] and Italy [37], the number of asthma patients among people with COVID-19 was much lower than expected. In another study of 1591 patients with COVID-19, only 4% had COPD but the form of asthma was much lower. In another study in New York, only 9% of people with COVID-19 had asthma [38], 14% in the UK [39] and 2 to 3% in Spain [40]. The results of a study confirm that patients with or without asthma

have no difference in COVID-19 disease severity (length of stay, maximal oxygen flow needed, noninvasive ventilation requirement, and intensive care unit transfer). It also does not appear to be a risk factor for severe SARS-CoV-2 pneumonia, since asthma is a disease of the upper respiratory tract. Besides, SARS-CoV-2 pneumonia is not an induction factor of asthma exacerbation [41]. The results of a review study by Mendes, et al, based on current medical records, concluded that 7.5% were diagnosed with asthma. All papers reviewed for correlations between asthma and COVID-19 showed that asthma was present in only 1.8% of patients and this number was much lower than expected compared to the global prevalence of asthma. According to the Global Asthma Report, 339 million people were diagnosed with asthma in 2018, which is related to 4.4% of the world's population, so asthma does not appear to be an important condition in COVID-19 patients or could be a protective factor [42]. Asthma is expected to be a risk factor for SARS-COVID2, while clinical data in COVID-19 wards are about 2 to 3% vs. 6% of the general population, and people with asthma appear to be less likely to develop SARS-COVID-2. This can be due to various factors, such as: 1- The anti-inflammatory effect exerted by ICS and their negative effect on cytokine storm 2 - Increased compliance with anti-asthma treatment due to fear of viral infection that disrupts the clinical course [43].

In term of treating asthma in the COVID-19, a 2020 study in the United Kingdom found that taking oral corticosteroids, which are the first line of treatment for asthma, was associated with a higher risk of death from COVID-19 in the hospital than people without the disease. It has been concluded that COVID-19 can be protected by optimizing the use of systemic corticosteroids and avoiding hospitalization [34]. Another study conducted in Belgium in 2020 by Maes, et al states that corticosteroids are the first-line treatment for asthma and may be affected by COVID-19 disease, and that long-term treatment with systemic corticosteroids because it weakens the immune system. Suppresses increases the risk of viral infections including COVID-19 [44]. A 2020 study in Maryland by Akenroye, et al found that the role of asthma and the increased severity of COVID-19 infection remains unclear, but there is concern among patients and caregivers that the COVID-19 virus is highly contagious. The upper extremities are related and there is a slight tendency for the lower airway to be contaminated with COVID-19 in healthy individuals, but the possibility of lower airway contamination in people with asthma may increase, and the study also showed that asthma medications do not interact with the COVID-19 [45].

Some studies suggest that due to overexpression of ACE2 in rhinovirus infections, and activation of ACE2 regulates many antiviral responses to cytokines [46]. This may lead to cytokines exacerbation which is COVID-19 pathological response. These results suggest that viral infections that cause worsening of asthma show synergistic bio molecular interactions due to COVID infection. On the other hand, clinical studies in different countries showed that, asthmatic patients with COVID-19 infection are small fraction of all infected patients [47]. According to the review, it is recommended that patients with asthma avoid abrupt discontinuation of their medications. This is especially important for corticosteroids. In this regard, due to the relative advantages of inhaled corticosteroids, they are preferable in comparison oral corticosteroids [48]. These patients should avoid a variety of allergens and factors that trigger asthma (like cold weather). It seems that further clinical and laboratory research are required for confirmation the supposed association between asthma and COVID-19 infection.

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