

the below respiratory tract which includes windpipe and lungs [3].

If we look toward asthma it is an inflammatory disease which is long term and involves obstruction of the airway and bronchospasm.

Factors responsible for the asthma are both genetic as well as environmental. It mostly involves bronchi and bronchioles and rarely the upper respiratory system (sinuses, throat and nose).

So it is more related to the lower respiratory tract rather to the upper respiratory system.

LITERATURE REVIEW

Pathophysiology of asthma and COVID-19 infection

Asthma: As discussed earlier, asthma leads to the inflammation of the bronchi and the bronchioles which increases the contractility of the smooth muscles that surrounds the organ.

This causes wheezing due to narrowing of the airway (caused by contraction of the smooth muscle).

There is increase in the number of eosinophil's and also the lamina reticular is thickens along with the increase in the number of mucous glands.

Components of the immune system that are involved in asthma are chemokine, cytokines, histamine and leukotriene's [4].

COVID-19: The SARS-CoV-2 virus infects a wide and large range of systems and the cells of the body.

The COVID-19 infection is most known for attacking the upper respiratory tract that includes the sinus, throat and nose and the lower respiratory tract that includes the lungs and windpipe The organ that is most affected by the infection is the lung as the spike protein which is present on the virus binds to the ACE-2 (Angiotensin Converting Enzyme) after which un-coating takes place which proceeds with replication of viral genomic RNA by RNA dependent RNA polymerase.

After this translation of viral proteins occurs and later on viral assembly takes place into the golgi apparatus and later exocytosis occurs. In this way the virus enters the organ and shows its effects [5].

People suffering from asthma are always at a high risk for not only Coronavirus but too many viral infections and thus can be a cause for acute as well as severe exacerbations of asthma. If we compare this with the patients admitted in hospital for influenza virus infection, it can be found that almost 25% population suffering from influenza; have had asthma sometime in their life [6].

So, this situation forced every healthcare worker to see that the population suffering from asthma should be taken care for Coronavirus as these people can get infected with virus very easily.

But, if we take a look towards global epidemiology of COVID-19 and asthma combination, it shows a complex picture. Survey carried in various regions including Spain, Arabia, Brazil, China, India, shows a lower prevalence of asthma in patients admitted for COVID-19 infection.

It was found in the USA, Australia and UK that there was high prevalence of asthma in patients admitted for COVID-19 infection [7].

It is very unclear whether asthma is related with the worst prognosis of COVID-19 infections.

A cohort follow up study was performed in France where almost 770 patients were infected with Coronavirus and about 38 patients were found to have asthma history. But it was found the patients suffering from asthma were not over presented and had minimal or normal COVID-19 symptoms rather than untreatable pneumonia [8].

And the patients who over presented the symptoms including pneumonia were not suffering/had no history of asthma.

Many surveys were carried out in different countries and in different regions and were found that patients suffering from asthma are not on an increased risk for severe COVID-19 infection.

In cohort study performed in Korea of nearly 7,350 patients suffering from COVID-19 infection, it was found that almost 10% patient had severe outcomes and over presented with symptoms and out of these 7% population was suffering from asthma and 3 percent population were without asthma [9].

This study also showed that the people with non-allergic asthma have greater risk of severe outcomes in COVID-19 infections rather than people having allergic asthma (type 2 asthma).

This data also shows that asthma condition is not totally responsible for the severity of COVID-19 infection.

In short we can come to the conclusion that there is much variability in the occurrence of asthma in patients with COVID-19 infection in different countries and in different regions. Asthma patients were not seen to have severe outcomes instead had lower or same clinical features compared to normal COVID-19 patients; this is because most asthmatic population are of allergic asthma and allergic asthma patients are at lower risk as compared to the non-allergic patients.

Till now the studies which we have seen have shown that asthma is connected with the severity of the infection and that too it involves about 14% of patients. But it is surprising to know that out of these patients also only patients having non allergic asthma were more on the severity side rather than allergic asthma patients [10].

And there wasn't any association between asthma and the death risk of patients on mechanical ventilation or intubation. So asthma cannot be considered as an independent or single factor responsible for the severity of asthma.

According to the survey done in Colorado university and hospital, it was concluded that the patients infected with Coronavirus and added with comorbidities like hypertension, chronic obstructive lung disease and diabetes had a bad prognosis as compared with the COVID-19 infected people having asthma as comorbidity [11].

This also shows that asthma cannot be taken as a single comorbidity which is responsible for the bad prognosis of the COVID-19 patient's in fact other non-pulmonary conditions like hypertension and diabetes play a major role in worsening the patient's condition.

Again looking towards cohort study conducted in Boston university, it was noticed that patients with asthma were not on increased risk for hospitalization, ICU, mechanical ventilation and risk of death.

Also according to the study carried in New York, asthma was not responsible for the worst outcome of the patients rather other non-pulmonary conditions were responsible for this condition.

According to the research on 600 patients, asthma was not responsible for the ICU admission, but the patients suffering from other obstructive lung diseases were at high risk of severe outcomes and most the patients were on ventilators and in ICU.

According to the survey carried out by morbidity and mortality weekly report, made a report of about 1500 patients admitted in USA for COVID-19 infections and it was found that only about 8% of infected population out of 1500 patients developed wheezing, which is less than 10% of asthmatic population in general [12].

This thus shows that COVID-19 infection rarely produces any asthmatic exacerbations during hospitalization. And also very less people developed asthma attacks during their stay in hospital during COVID-19 infection.

DISCUSSION

COVID-19 and moderate severe asthma

A small group of patients with asthma (10%) can have poorly controlled asthma instead of taking long treatment, this group can be considered as more prone for developing severe form of asthma, but there is very less data available to know this hypothesis.

According to the study in USA, people with moderate to severe asthma are at a higher risk for developing worst outcomes of COVID-19 infection.

And according to the survey carried out in USA, it showed that the situation of infection was worst in people who were taking oral corticosteroids before for asthma. Need to take oral corticosteroids for asthma shows that the asthma of the patient was in the moderate to severe category and was not responsible simple drug treatment; again it proved that COVID-19 infection can get worse in people suffering with moderate to severe form of asthma.

According to the Korean study, asthma was not associated with the mortality but the history of acute exacerbations of asthma was related to the mortality of the COVID-19 patient. Also people with step 5 asthma are at higher risk for development of infection and also equally.

And also asthmatic treated with biologics has no effects on the outcome of the disease [13]. Through all this discussion it is much clear that the comorbidities like cardiovascular diseases, age, obesity, diabetes are more responsible for the worsening of the disease, rather than asthma.

The severity of the infection does not only depend on asthma itself but also the type of asthma, phenotypes and genotypes of asthma, medicines in asthma and also asthma with what comorbidities.

Asthma protection against the worst outcome of COVID-19 infection

Many theories, survey, studies have suggested that asthma can also act as a protective covering against the poor prognosis of COVID-19 infections [14].

Many mechanisms are thought to be applicable for the same, like:

- Viral entry receptor expressions.
- Type 2 inflammation.
- Age factor.
- Use of asthma treatment (adherence to the ICS therapy)
- Presence of comorbidities.
- Decreased exposure.

Viral entry and receptor expression

Every virus or bacteria has its own way/path for entering into the desired cells or location, for example if we talk about Rhinovirus uses the intercellular adhesion molecule I for the entry into the desired cells.

In the same way Coronavirus makes use of the cell receptors that are present in high numbers in the oral mucosa and in the airways that is Angiotensin Converting Enzyme-2 (ACE-2), these are responsible for all clinical features and the lung injury that occurs in COVID-19 patients.

The cofactors that facilitates the expression of virus or the cofactors which helps in increasing the infectivity are the Trans membrane peptidase serine and the protease, these help in the cleavage of the protein (spike protein) of the virus that helps in the entry into the host cells.

According to the survey done, it was found that in the population of asthmatic people, those who were old aged, had diabetes and more of African American race has large expression of both ACE-2 and TMPRSS 2 [15].

While the patients who were on ICS, showed low expression of ACE-2 and TMPRSS 2.

And also, low expression was found in the patients who had allergic asthma rather than in patients who had non allergic asthma.

Expression of IL 13 also lowers the expression of the same cofactors. This clearly gives us a view that allergic asthma has some protection against the COVID-19 infection as it lowers the expression of the cofactors like ACE-2 and TMPRSS 2.

Yes not only allergic and non-allergic asthma are factors but the age, other comorbidities, sex, race, all things matters.

Role of eosinophil's

Eosinophil's plays a major role in clearing the viral load. And also the host defence against the virus.

People infected with Coronavirus have less eosinophil in their blood and eosinophils are always raised in a patient who has asthma.

So raised eosinophil's in asthmatic can become helpful in COVID-19 infection to fulfil the loss of eosinophils and thus protective against the COVID-19 infection.

Those patients having asthma and also low eosinophilic count are at a high risk of COVID-19 infection and its worst outcomes.

Blood eosinophilic count of peripheral blood should be done to know the prognosis of COVID-19 infection [16].

Patient's death can also be due to thrombocytopenia, hypoxemia, raised IL 6, C-reactive protein, D-dimer levels, ferritin etc.

Age

Age is also an important factor in the prognosis of COVID-19 infection.

In a study it was found that the younger people suffering from COVID-19 infection were presented with rhinitis and eczema and those who were older and had infection were having comorbidities like hypertension and diabetes.

Younger generation with asthma and COVID-19 infections were found to be safe as, the asthma was mostly allergic and thus has a presentation of IL 4, IL 13 and also the expression of eosinophil's, which acts as a protection against the infection.

Thus the younger generation suffering from COVID-19 infections are on safe side [17].

Where older populations with non-type 2 asthma and COVID-19 infection with some comorbidities like hypertension and diabetes has worst outcomes because there is no expression of IL and eosinophil's and thus offers no protection to the respiratory epithelium and thus can lead to high degree of inflammatory response and thus causing lung injury.

Thus age factor also plays an important role in COVID-19 infections.

Protective shielding decreased exposure to virus

In COVID-19 pandemic many rules and regulations were made in concern with the infection, limiting the exposure of person to the virus. Thus this also leads to the decreased exposure of person to the environmental allergens and thus was decrease in the asthma patients in hospitals as a secondary effect.

Sticking to the therapy

As far as hospitalization for asthma is concerned. There was decrease in hospitalization for asthma in this pandemic. It was believed that COVID-19 will increase the asthma attacks in people, but it has encouraged people to take preventive measures in order to stay safe from COVID-19 infections. People have learned to keep their environment safe and clean and allergen free, some have started to quit smoking has learned to take preventive measures and medications to be safe from infections. All this changes are helping people to fight against allergic asthma and thus have lesser hospitalization compared to before pandemic time.

Asthmatic therapy and COVID-19

If any patient suffering from asthma is taking inhaled corticosteroids, it is always recommended to continue and don't stop. People on long term use of inhaled corticosteroids are at a risk for worsening of COVID-19 infection as their asthma is poorly controlled, but this does not mean that all people on ICS will have worse infections [18]. ICS may also act as a protective agent for the infection, as it reduces the inflammation in the lungs, with minimal side effects. High dose of inhaled corticosteroids are aimed at the inflammation in the lungs, but the moderate immunosuppression can also be done as it has both systemic and local bioactivity. Apart from the anti-inflammatory action of the ICS, have been found to have antiviral effects also. Thus the treatment with ICS should be continued in COVID-19 infection.

COVID-19 infection and biological therapy

It is very challenging to manage patients with severe asthma in pandemic. It is recommended to keep biological therapy for the patients in COVID-19 pandemic. Biological therapy is mostly use for the people who are not manageable with other treatments [19]. This infection can lead to eosinopenia, and there are many reasons for the same like altered or decreased eosinophilopoiesis, apoptosis (induced by 1I FN which is released during acute infection).

Allergen immunotherapy and COVID-19

This biological therapy has been in use since many years and has found to be preventive against COVID infection. This therapy to patients becomes useful if worked properly. It is must for the people who suffers from allergies and also have infected with COVID-19 infections. The main aim of the treatment is generation and maintenance regulator B cells and regulatory T cells [20]. Regulatory T cells play a crucial role in infection by

limiting cytokine storm and decreasing the tissue damage [21-35]. Thus this therapy has a protective role against COVID infections as it helps in controlling the cytokines storm.

CONCLUSION

Based on the studies and surveys it is very clear that asthma does not increase the risk for COVID-19 infections nor it leads to the worst progression of the disease. Asthma can be taken as a risk factor for COVID-19 infections, only if it is accommodated by other factors like smoking and other comorbidities like diabetes, hypertension, and chronic pulmonary disease. According to type of asthma, people with allergic asthma are less prone for the severity of COVID-19 infection while those with non-allergic asthma are at a greater risk for the worsening of the COVID-19 infection. All asthmatic patients should keep taking their treatment, whether it's biological therapy or the use of ICS. It does not increase the susceptibility to COVID-19 infections. Further clinical and experimental studies are necessary for finding the exact relationship between asthma and COVID-19 infection.

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