IJPSR (2021), Volume 12, Issue 7 **(Review Article)**

INTERNATIONAL JOURNAL OF PHARMACEUTICAL SCIENCES AND RESEARCH

Received on 08 October 2020; received in revised form, 22 May 2021; accepted, 10 June 2021; published 01 July 2021

PATHOPHYSIOLOGICAL ASSOCIATION OF COVID-19 WITH TYPE I DIABETES MELLITUS AND ASTHMA IN THE PEDIATRIC POPULATION AND ITS MANAGEMENT STRATEGY

Tippaluru Spurthi [1], Muthuraja Mathivanan Koushik [2] and M. G. Rajanandh [*3]

Department of Pharmacy Practice [1], Creative Education Society's College of Pharmacy, Chinna Tekuru, Kurnool - 518218, Andhra Pradesh, India.
Department of Respiratory Medicine [2], Sri Ramachandra Medical College and Research Institute, Sri Ramachandra Institute of Higher Education and Research (SRIHER), Deemed to be University (DU), Porur, Chennai - 600116, Tamil Nadu, India.
Department of Pharmacy Practice [3], Sri Ramachandra Faculty of Pharmacy, Sri Ramachandra Institute of Higher Education and Research, Deemed University, Porur, Chennai - 600116, Tamil Nadu, India.

Keywords:

Angiotensin-converting enzyme, Adherence, Comorbidity, Inhaled corticosteroids, Insulin

Correspondence to Author:
Dr. M. G. Rajanandh

Department of Pharmacy Practice, Sri Ramachandra Faculty of Pharmacy, Sri Ramachandra Institute of Higher Education and Research, Deemed to be University, Porur, Chennai - 600 116, India

E-mail: rajanandh.mg@sriramachandra.edu.in

ABSTRACT: Background and Aim: Coronavirus 2019 (COVID-19) is a pervasive emergency affecting 1-5% of children, among whom the majority are with preexisting comorbidities. This commentary aim is to highlight two such prominent childhood comorbidities, *i.e.*, asthma and type 1 diabetes mellitus (T1-DM), with their pathophysiological link to COVID-19. **Method:** We searched the Google Scholar and PubMed databases till August 15, 2020, and retrieved the data connected to our aim for reviewing. **Results:** Asthma and T1-DM in children affect the COVID-19 progression due to their interlinked disease mechanisms with infection. Th-2 (T-helper) low endotype asthma and TI-DM connect by decreased ACE (angiotensin-converting enzyme) receptor expression, whereas Th-2 high endotype intensifies the COVID-19 *via* declining the IFNs (interferons) related anti-viral effect. Addressing these comorbidities therapeutically in this pandemic includes continuity in respective disease control treatment plans with the use of pressurized metered-dose inhaler (pMDI) with a spacer rather than nebulizers or keeping the low incidence of exacerbations by inhaled/oral corticosteroid and/or Montelukast in children with asthma is recommended. In the case of T1-DM, blood glucose of 70-144mg/dL and <0.6 mmol/L of blood ketone levels to be maintained without stopping Insulin dosing should be followed. **Conclusion:** Elevating the immunity with regular telemedicine and proper adherence to a prescribed action plan can address the present state of infection in children with asthma or T1-DM, or both.

INTRODUCTION: Coronavirus disease (COVID-19) caused by Severe Acute Respiratory Syndrome Coronavirus-2 (SARS-CoV-2), affecting the older age in prominence due to their weaker immune system and with high comorbidity risk [1-2].

QUICK RESPONSE CODE

DOI: 10.13040/IJPSR.0975-8232.12(7).3618-21

This article can be accessed online on www.ijpsr.com

DOI link: http://dx.doi.org/10.13040/IJPSR.0975-8232.12(7).3618-21

Even the primary event that leads to this pandemic crisis is not clear; the world health organization (WHO) described it as Public Health Emergency of International Concern (PHEIC), affecting throughout 213 countries and territories [3, 4]. Around 21.83 million confirmed cases worldwide were reported at the time of writing this article, with India (2.6 million cases) standing in the third position after the United States of America (USA) and Brazil [4].

The infection had a zoonotic spread affecting all age groups *via* inhalation of infected patient's respiratory droplets or touching the contaminated

surfaces. The disease has a three-stage progression, restricting the infection to the mild stage, affecting the upper respiratory conducting zone organs like sinuses, nose, and throat in 80% of patients [1, 5]. Host innate immune response involving the cytokine activity plays a key role in deciding the clinical outcome in the remaining 20% of infected patients, advancing to stage 3, *i.e.,* Acute Respiratory Distress Syndrome (ARDS) [1]. These serious SARS-CoV-2 infection symptoms are presented mostly in adults but do not rule out the fact that children are considered as silent spreaders with a high viral load. Whereas in the younger population, the disease stays milder or asymptomatic due to various postulated mechanisms all centered towards low immune-related receptors as they are still under matured [6]. A report by the European Centre for Disease Prevention and Control summarizes that the symptomatic kid dismisses the same amount of virus as an infected adult [7]. India has reported only 1% of mortality in age below 14 years but consists around 35.3% of proportion in that age group, pointing out the fact of detailed studies needed in this section of the population [8].

Out of the little data available in children, it was noticed that infection is mostly less aggressive or asymptomatic, wherein later case testing is not done as a child is with no symptoms but can still transmit the disease [6]. The transmission is likely due to secondary cases, *i.e.*, exposure to a positive adult[7]. In the case of comorbidity risk, children also show a similar pattern which was postulated from the results of a multi-centered cross-sectional study in COVID-19 positive children belonging to North American states. Nearly 83% were presented with pre-existing medical conditions. Apart from the first two major comorbidities related to genetic or developmental anomalies and malignancy or immunosuppressed conditions, obesity and diabetes account for the next 18% of conditions followed by anemia chronic lung diseases [9]. In another few systemic reviews also, it was significantly mentioned that children with diabetes and asthma are prone to a higher risk of disease severity [10-11].

Considering these details and combining the epidemiological information, asthma and TI-DM are observed as two chronic illnesses affecting childhood, especially the school-bearing age groups, with a prevalence range from 3.5-29.5% and 1.28 lakh of cases, respectively [12-13]. The link between these autoimmune and atopic conditions was the understudy for ages, referring to a positive and negative correlation. The T-cell mediated immune responses played a key role in their pathophysiology, also interplayed with genetic predisposition and environmental factors [14]. A pediatric case-cohort study also outlined a significant risk of developing T1-DM in previously diagnosed asthmatic children to support the link with one another [15]. Since these comorbidities are interrelated and if children with either asthma or T1-DM or both together are exposed to COVID-19, then the risk of virus progression can be mediated physiologically by diminished expression of ACE receptors in both T1-DM and Th-2 low endotype asthma. Whereas in Th-2 high asthma patients, the aggravated inflammatory responses over the IFNs mediated anti-viral activity leading to increased viral load (See **Fig. 1** for the proposed patho-physiological link in detail) [16-18].

As this global threat is transforming its nature rapidly, detailing the management options by the guidelines proposed by the Centers for Disease Control and Prevention (CDC), World health organization (WHO), and Global Initiative for Asthma (GINA) Update in March 2020, in these specific sets of children would be adding a helping hand for addressing the future possibility in the course of risk management **(See Table 1)** [16, 19-20].

In summary, the COVID-19 in children seemed to have a milder infection, but mostly as per the literature, show an equal risk of transmission as adults. In addition to this, the majority of children with positive infection confirmed with pre-existing comorbidities. Asthma and T1DM are two such chronic childhood disorders whose disease physiology is strongly associated with SARS-CoV-2 infection's pathophysiology involving diminished anti-viral response and ACE receptor depressed activity, respectively, marking them the prime risk factors to be studied further in estimating the prospects in children. Risk ratios may elevate if the child is presented with both asthma and T1-DM together, as prominent evidence in developing T1DM among those with asthma was reported based on their common genetic predispositions and environmental factors. Following the guidelines proposed by CDC or GINA-COVID-19 update

2020, boosting immunity and avoiding viral exposure along with continuity in management plan with regular telemedicine circumvent the untoward risk in the pediatric population. On the bright side, the lockdown in the course of a pandemic is aiding the reduced exposure to outside allergic triggers in asthmatic children and increasing the parental monitoring in regard to a balanced diet, physical activity, psychological stress, and medication adherence.

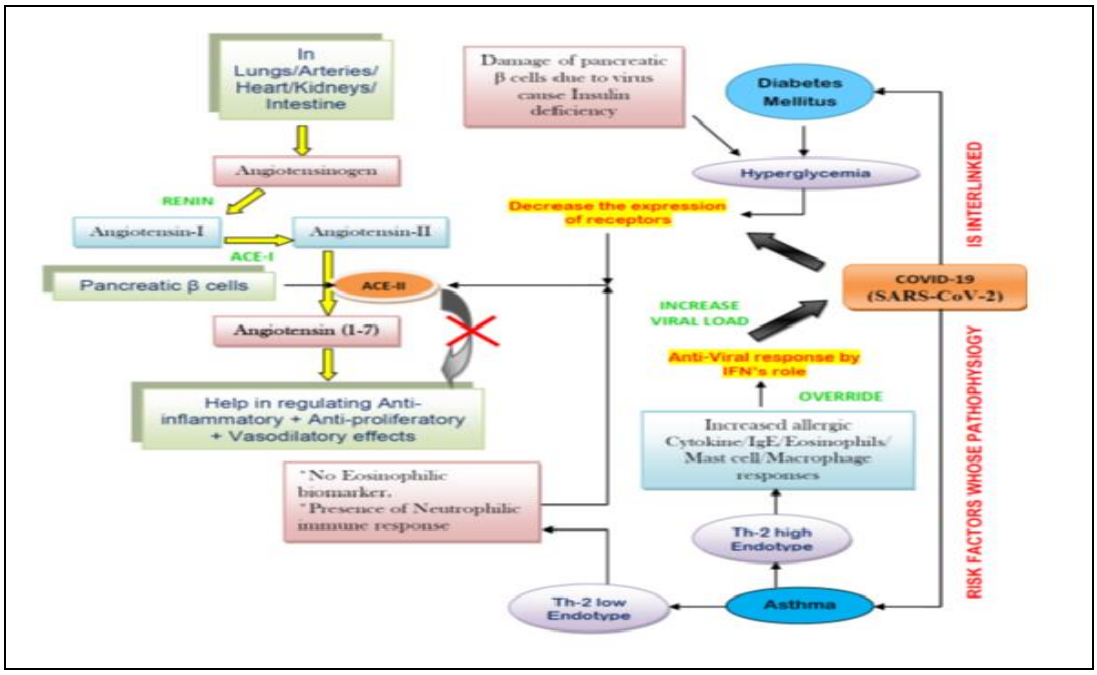

FIG. 1: COVID-19 PATHOPHYSIOLOGY IN ASSOCIATION WITH ITS RISK FACTORS ASTHMA AND DIABETES MELLITUS. Abbreviations: ACE: angiotensin-converting enzyme; COVID-19: coronavirus disease 2019; IgE: immunoglobulin type E; IFN's: interferon; Th-2: T-helper cells; SARS-CoV-2: severe acute respiratory syndrome coronavirus.

TABLE 1: POSSIBLE MANAGEMENT OPTIONS FOR TREATING T1-DM AND ASTHMA IN THE COVID-19 CRISIS

T1-DM	Common for both	Asthma
Continue regular Insulin dosing prescribed as per the treatment plan.	Reduce the exposure to COVID-19 virus by - Effective follow of rules & regulations related to lockdown.	Continue regular inhaled medications, including CS prescribed as per the treatment plan.
Maintain the plasma glucose levels in between 72-144 mg/ dL orHbA1c < 7%.		Preventive therapy for exacerbations including Inhaled CS ± Montelukast. *
Go on with in-house nutritious diet, physical activity, and psychological support under parental guidance.	Use of telephonic mode for communicating with physicians.	In *acute attack*- can use oral CS.**
Monitor hypoglycemia either due to prescribed insulin dosing or use of Chloroquine/Hydroxychloroquine as a part of prophylaxis in COVID-19 infection.	Online drug delivery to home with proper safety measures.	In *severe attack*- Long-term use of oral CS± inhaled medications. #
	Proper care by parents exposed outside using regular sanitization methods.	Nebulizer use is restricted to avoid viral dissemination.
		Alternate pMDI *via* a spacer or dry powder inhaler can be used.

Abbreviations: COVID-19 - coronavirus disease 2019; CS - corticosteroids; DKA - diabetic ketoacidosis; HbA_{1c} - glycated hemoglobin; pMDI - pressurized metered-dose inhaler; *Only under medical prescription; **This should be only given after medical prescription to prevent untoward risk; #The oral CS dose should be at low or else alternate use of biological agents can be planned under medical prescription only. During this maintenance, asthma treatment as per the prescribed asthma action plan should be continued. ##Urine test strips or blood ketone monitoring meter should be used to maintain < 0.6 mmol/L blood ketone level. Extra insulin dosing can be planned by contacting the physician if the levels are high for >24hrs and always make sure the child is hydrated with sugar-free liquids to avoid dehydration.

CONCLUSION: Finally, this prodigious spread of infection day-by-day, along with the indefinite time frame in successful vaccine development creates fear and ambiguity in children with socio-economic constraints. Even children account for a less percentage in the prevalence of the disease, further

studies in Indian children affected by COVID-19 and their connected demographic, socio-economic, developmental, medical, and psychological factors pave effective future clinical outcomes.

FUNDING: None

ACKNOWLEDGEMENT: Nil

DECLARATION OF COMPETING INTEREST: No conflict of interest to declare.

REFERENCES:

1. Balasubramanian S, Rao NM, Goenka A, Roderick M and Ramanan AV: Coronavirus Disease 2019 (COVID-19) in Children - What We Know So Far and What We Do Not. Indian Pediatrics 2020; 57: 435-42.
2. Massachusetts General Hospital. [INTERNET]. [Updated 2020 Mar/Apr 04; cited 2020 Aug 17]. Available from: https://www.massgeneral.org/assets/MGH/pdf/news/coronavirus/risk-factors-for-severe-COVID-19.pdf.
3. Chatterjee P, Nagi N, Agarwal A, Das B, Banerjee S and Sarkar S: The 2019 novel coronavirus disease (COVID-19) pandemic: A review of the current evidence. Indian J Med Res 2020; 151(2 & 3): 147-59.
4. Worldometer. COVID-19 Coronavirus pandemic. [INTERNET]. [Updated 2020 Aug 17; cited 2020 Aug 17]. Available from: https://www.worldometers.info/coronavirus/
5. Yuki K, Fujiogi M and Koutsogiannaki S: COVID-19 pathophysiology: A review. Clin Immunol 2020; 215: 108427.
6. Yonker LM, Neilan AM and Bartsch Y: Pediatric SARS-CoV-2: Clinical Presentation, Infectivity, and Immune Responses [published online ahead of print, 2020 Aug 20]. J Pediatr 2020; doi: 10.1016/j.jpeds.2020.08.037.
7. European Centre for Disease Prevention and Control. COVID-19 in children and the role of school settings in COVID-19 transmission. [INTERNET]. [Updated 2020 Aug 06; cited 2020 Aug 17]. Available from: https://www.ecdc.europa.eu/en/publications-data/children-and-school-settings-covid-19-transmission.
8. Union Ministry of Health & Family welfare. 18th meeting of the high-level Group of Ministers (GoM) on COVID-19. [INTERNET]. [Updated 2020 Jul 09; cited 2020 Aug 17]. Available from: https://pib.gov.in/PressReleasePage.aspx?PRID=1637517#:~:text=The%2018th%20meeting%20of%20the,He%20was%20joined%20by%20Dr.
9. Shekerdemian LS, Mahmood NR and Wolfe KK: Characteristics and Outcomes of Children with Coronavirus Disease 2019 (COVID-19) Infection Admitted to US and Canadian Pediatric Intensive Care Units [published online ahead of print, 2020 May11]. JAMAPediatr.2020;10.1001/jamapediatrics.2020.1948.doi :10.1001/jamapediatrics 2020.1948.
10. CDC COVID-19 Response Team. Coronavirus Disease 2019 in Children - United States, February 12-April 2, 2020. MMWR Morb Mortal Wkly Rep. 2020; 69(14):422-426. doi:10.15585/mmwr.mm6914e4.
11. Saleem H, Rahman J, Aslam N, Murtazaliev S and Khan S: Coronavirus Disease 2019 (COVID-19) in Children: Vulnerable or Spared? A Systematic Review. Cureus 2020; 12(5): e8207.
12. Global asthma network. The Global Asthma report 2018. [INTERNET]. [Updated 2018 Aug 31; cited 2020 Aug 23]. Available from: http://www.globalasthmareport.org/resources/global_asthma_report_2018.pdf.
13. Virmani A. Type 1 Diabetes in India: The Numbers Show the Way Ahead. Indian Pediatr. 2019;56(3):189-190.
14. Hörtenhuber T, Kiess W and Fröhlich-Reiterer E: Asthma in children and adolescents with type 1 diabetes in Germany and Austria: Frequency and metabolic control. Pediatr Diabetes 2018; 19(4): 727-32.
15. Metsälä J, Lundqvist A and Virta LJ: The association between asthma and type 1 diabetes: a paediatric case-cohort study in Finland, years 1981-2009. Int J Epidemiol 2018; 47(2): 409-16.
16. Bornstein SR, Rubino F and Khunti K: Practical recommendations for the management of diabetes in patients with COVID-19. Lancet Diabetes Endocrinol 2020; 8(6): 546-50.
17. Liu S, Zhi Y and Ying S: COVID-19 and Asthma: Reflection during the Pandemic. Clin Rev Allergy Immunol 2020; 59(1): 78-88.
18. Camiolo M, Gauthier M, Kaminski N, Ray A and Wenzel SE: Expression of SARS-CoV-2 receptor ACE2 and coincident host response signature varies by asthma inflammatory phenotype. J Allergy Clin Immunol. 2020; 146(2): 315-324.
19. Chowdhury S and Goswami S: COVID-19 and type 1 diabetes: dealing with the difficult duo [published online ahead of print, 2020 Jul 14]. Int J Diabetes Dev Ctries 2020; 1-6.
20. Global Initiative for Asthma (GINA). COVID-19: GINA answers to frequently asked questions on Asthma management. [INTERNET]. [Updated 2020 Mar 25; cited 2020 Aug 17]. Available from: https://ginasthma.org/covid-19-gina-answers-to-frequently-asked-questions-on-asthma-management/.

How to cite this article:
Spurthi T, Koushik MM and Rajanandh MG: Pathophysiological association of Covid-19 with type i diabetes mellitus and asthma in the pediatric population and its management strategy. Int J Pharm Sci & Res 2021; 12(7): 3618-21. doi: 10.13040/IJPSR.0975-8232.12(7).3618-21.