International Journal of Research and Review
Volume 11; Issue: 10; October 2024
Website: www.ijrrjournal.com
Review Article *E-ISSN: 2349-9788; P-ISSN: 2454-2237*

Association of Chronic Obstructive Pulmonary Disease Exacerbation with Type-2 Diabetes Mellitus Comorbidity: Possibility Role of IL-8

Armita Dewi[1], Faisal Yunus[2], Nirwana Fitriani Walenna[3], Irawaty Djaharuddin[4], Arif Santoso[5], Nur Ahmad Tabri[6], Muhammad Ilyas[7]

[1] Department of Pulmonology and Respiratory Medicine, Faculty of Medicine, University of Hasanuddin, Wahidin Sudirohusodo Hospital, South Sulawesi, Indonesia
[2] Department of Pulmonology and Respiratory Medicine, Faculty of Medicine, University of Indonesia, Persahabatan Hospital, Jakarta, Indonesia
[3] Department of Anatomy, Faculty of Medicine, University of Hasanuddin, South Sulawesi, Indonesia.
[4]Department of Pulmonology and Respiratory Medicine, Faculty of Medicine, University of Hasanuddin, Wahidin Sudirohusodo Hospital, South Sulawesi, Indonesia
[5]Departement of Pulmonology and Respiratory Medicine, Faculty of Medicine, University of Hasanuddin, Wahidin Sudirohusodo Hospital, South Sulawesi, Indonesia
[6] Department of Pulmonology and Respiratory Medicine, Faculty of Medicine, University of Hasanuddin, Wahidin Sudirohusodo Hospital, South Sulawesi, Indonesia
[7]Departement of Pulmonology and Respiratory Medicine, Faculty of Medicine, University of Hasanuddin, Wahidin Sudirohusodo Hospital, South Sulawesi, Indonesia

Corresponding Author: Armita Dewi

DOI: https://doi.org/10.52403/ijrr.20241039

ABSTRACT

Introduction: Type-2 Diabetes Mellitus (type-2 DM) is associated with the incidence of respiratory tract infections which is a risk factor for Chronic Obstructive Pulmonary Disease (COPD) exacerbations. Interleukin-8 (IL-8) is one of inflammatory mediators both in COPD exacerbation and pathogenesis of type 2 DM.
Method: We conducted literature searched in online database PUBMED and Google Sholar, all study published since 2015 until 2024.
Conclusions: IL-8 is a proinflammatory cytokine that has been shown to play a role in COPD because it triggers mucus hypersecretion and bacterial colonization which is risk factor for exacerbation of COPD and causes adipose tissue dysfunction in type 2 diabetes.

Keywords: COPD exacerbation; type-2 DM; prevalence; IL-8

1. INTRODUCTION

Chronic Obstructive Pulmonary Disease (COPD) is a major cause of death and illness worldwide which causes a significant increase in the economic and social burden on society.1 COPD is associated with several comorbidities including cardiovascular and cerebrovascular diseases, osteoporosis, depression, lung cancer, and diabetes mellitus. (DM). Comorbidities increase the frequency of hospitalization for COPD patients, thereby increasing the cost of care.2

2. ASSOCIATION OF COPD EXACERBATION AND TYPE-2 DM

Seven studies conducted in this review article report COPD exacerbations with type-2 DM comorbidity. The population of exacerbating COPD with comorbid type 2 DM varied in each study as many as 14-18442 with a prevalence of 21.79%-54.55%. This shows that the incidence of comorbid type 2 DM in COPD exacerbations is quite high.[3-9]

Symptoms of COPD exacerbation are characterized by an increased shortness of breath, increased sputum production, and changes in sputum color. Exacerbations according to Anthonisen's criteria were divided into three types. Type I or severe exacerbation has all the symptoms of an exacerbation, type II or moderate exacerbation has two of the symptoms of exacerbation, and type III or mild exacerbation has one of the symptoms of an exacerbation plus an upper respiratory tract infection of more than 5 days, unexplained fever, increased cough, wheezing or an increase in respiratory rate of more than 20% of baseline or pulse rate of more than 20%.[1]

Several factors contribute to the association between acute exacerbation of COPD and type-2 DM and its complications. Lin et al 2021 reported that the use of high doses of corticosteroids in the treatment of acute exacerbations of COPD led to an increase in the incidence and progression of hyperglycemia.[10] In addition, type-2 DM can increase the incidence of pulmonary infections, which is a major risk factor for acute exacerbations of COPD. stimulate bacterial growth or stimulate bacterial binding to the airway epithelium.[11]

Philips et al (2003) in their study demonstrated that local glucose concentrations in human airway secretions are usually very low.[12] However, when blood glucose is raised above the threshold of 6.7-9.7 mmol/l, glucose becomes detectable in airway secretions. at a concentration of 1-11 mmol/l.[12,13] Hyperglycemia associated with high glucose levels in respiratory secretions can predispose to respiratory tract infections that trigger bacterial growth and impair local innate immunity that suppresses the host's response to infection.[14]

3. ROLE OF IL-8 IN COPD EXACERBATION AND TYPE-2 DM COMORBIDITY

Exposure to cigarette smoke, harmful gases, or particles for a long time can cause complex pathological changes in the airways and lung parenchyma, resulting in worsening of respiratory function due to inflammation of the lower airways, fibrosis of the airway walls, smooth muscle hypertrophy, goblet cell hyperplasia, mucus hypersecretion. and lung parenchymal damage.[15]

Inflammatory mediators that have been shown to increase in COPD patients are chemotactic factors that attract inflammatory cells from the circulation in the form of lipid mediators (leukotriene B4 which attracts neutrophils and T lymphocytes), chemokines (interleukin-8/IL-8 which attracts neutrophils and monocytes, amplifying the inflammatory process). and contribute to systemic effects (proinflammatory cytokines such as tumor necrosis factor-α, IL-β, and IL-6) and growth factors that promote structural changes (TGF-β leading to fibrosis in the peripheral airways).[1]

Interleukin-8 (IL-8) is a powerful incorporated neutrophil chemoattractant belonging to the CXC family. IL-8 is one of the mediators of the inflammatory response. IL-8 is produced and released by bronchial epithelial cells, monocytes, macrophages, and neutrophils. The main function of IL-8 in the activation and recruitment of neutrophils to sites of infection or injury.[16,17,18]

The increase in serum IL-8 levels in COPD, especially in the exacerbation phase, can be influenced by many things, such as the degree of obstruction, severity, and comorbidities. Infectious conditions can increase serum IL-8 levels. When there is an increase in bacterial colonization, it causes over-expression of adhesion molecules which then results in increased neutrophil adhesion and aggregation, increasing the expression of neutrophil elastase, all of which will trigger exacerbations.[19,20]

Zhang et al in 2018 found a positive correlation between the serum level of IL-8, and the serum levels of IL-6 and TNF-alfa. IL-8 increased mucus secretion by increasing the expression of genes encoding mucins (MUC5AC and MUCB) and resulted in airway smooth muscle contraction (22,23), which explains the lung function deterioration in the current study of patients with AECOPD. [22]

Yusuf (2019) reported from 65 subjects with COPD exacerbation, and 55 subjects with bacterial colonization sputum cultures were examined. The mean of IL-8 serum was significantly higher in the group with colonization than in the group without colonization (197.7 vs 131.2) with ($p<0.01$). The study shows a significant correlation between bacterial colonization with high serum IL-8 levels which play a role in the inflammatory process of the lower airway and an increase in the degree of pulmonary obstruction.[20]

Peripheral pulmonary inflammation in COPD causes a spillover of proinflammatory cytokines such as Tumor necrosis factor-α (TNF-α), Nuclear factor kappa B (NF-κB), Interleukin-1 beta(IL-1β), and Interleukin-6 (IL-6) and C-reactive protein (CRP) into the systemic circulation. TNF-α and IL-6 block insulin receptors, causing insulin resistance and an increased risk of type-2 diabetes.[15]

IL-8 is also a chemokine involved in systemic inflammation and activation in adipose tissue and may play an important role in the pathogenesis of type-DM. IL-8 also causes infiltration of macrophages in adipose tissue which data induces local and systemic inflammation. [19,21]

In type-2 DM patients, increased serum IL-8 levels correlated with higher IL-6 and TNF-α. Higher IL-8 levels correlated with worse glycemic control and with lower serum concentration of adiponectin.21 Adipose tissue acts as an endocrine organ and plays a role in the immune system which secretes many bioactive peptides that can affect insulin action. Ultimately, these inflammatory mediators lead to adipose tissue dysfunction and insulin resistance.[19,20]

Another possible link mechanism of COPD with type-2 DM is hypoxia-induced insulin resistance. Hypoxia stimulated HIF-1 α and -2 α protein expression and inhibited insulin-induced receptor and insulin receptor substrate tyrosine phosphorylation. Hypoxia dysregulates the expression of some adipokines and proinflammatory cytokines such as leptin, adiponectin, IL-1β, and IL-6.[22] Increased IL-8 concentration correlated with higher IL-6, TNF-α, fasting blood glucose with lower adiponectin concentrations.[23]

4. CONCLUSION

TNF-, IL-1β, IL-6, and CRP are released into the systemic circulation in COPD and block insulin receptors which then cause insulin resistance. IL-8 is a proinflammatory cytokine that has been shown to play a role in COPD because it triggers mucus hypersecretion and bacterial colonization which is one of the risk factors for exacerbations and causes adipose tissue dysfunction in type 2 diabetes.

Therefore, the future study must investigate the role of IL-8 and serum IL-8 levels in exacerbating COPD patients with comorbid type-2 DM for therapy and better patient management.

Declaration by Authors

Ethical Approval: Not Required

Acknowledgement: None

Source of Funding: None

Conflict of Interest: The authors declare no conflict of interest.

REFERENCES

1. Perhimpunan Dokter Paru Indonesia. PPOK (Penyakit Paru Obstruktif Kronik). Diagnosis dan Penatalaksanaan. Jakarta: Perhimpunan Dokter Paru Indonesia; 2016:1-78.
2. Miller J, Edwads LD, Agusti A, Bakke O, Calverley PMA, Celli B, et all. Comorbodity, systemic inflammation and outcomes in the ECLIPSE cohort. Resp Med, 2013;107(9): 1376-84.
3. Papathanassiou, E, Papaioannou A.I, Papanikkolau, I, Antonakis E, Makou I, Hillas G, et al. Glycated Hemoglobin (HbA1c) as a Predictor of Outcomes during Acute Exacerbations of Chronic Obstructive Pulmonary Disease. COPD: Journal of Chronic Obstructive Pulmonary Disease. 2021; 18:219–25.
4. Lin L, Shi J, Kang J, Wang Q. Analysis of prevalence and prognosis of type 2 diabetes mellitus in patients with acute exacerbation of COPD. BMC Pulm Med. 2021;21(1):7.
5. Koskela, H. O., Salonen, P. H., Romppanen, J., & Niskanen, L. A history of diabetes but not hyperglycaemia during exacerbation of

obstructive lung disease has impact on long-term mortality: A prospective, observational cohort study. BMJ Open 2015;5: e006794.
6. Annavarapu S, Goldfarb S, Gelb M, Moretz C, Renda A, Kaila S. Development and validation of a predictive model to identify patients at risk of severe COPD exacerbations using administrative claims data. Int J Chron Obstruct Pulmon Dis. 2018; 13:2121-30.
7. Figueira Gonçalves, J. M., García Bello, M. Á., Golpe, R., Alonso Jerez, J. L., & García-Talavera. Impact of diabetes mellitus on the risk of severe exacerbation in patients with chronic obstructive pulmonary disease. Clin Resp Jour. 2020;14(12):1208-11.
8. Mekov, E. V., Slavova, Y. G., Genova, M. P., Tsakova, A. D., Kostadinov, D. T., Minchev, D, et al. Diabetes Mellitus Type 2 in Hospitalized COPD Patients: Impact on Quality of Life and Lung Function. Folia Medica. 2016;58(1):36-41.
9. Mekov, E., Slavova, Y., Tsakova, A., Genova, M., Kostadinov, D., Minchev, D., & Marinova, D. (2015). Metabolic syndrome in hospitalized patients with chronic obstructive pulmonary disease. PeerJ, 2015;7.
10. Lin L, Shi J, Kang J, Wang Q. Analysis of prevalence and prognosis of type 2 diabetes mellitus in patients with acute exacerbation of COPD. BMC Pulm Med. 2021;21(1):7.
11. Gläser S, Krüger S, Merkel M, Bramlage P, Herth FJ. Chronic obstructive pulmonary disease and diabetes mellitus: a systematic review of the literature. Respiration. 2015;89(3):253-64.
12. Philips B J, Meguer J - X, Redman J.*et al* Factors determining the appearance of glucose in upper and lower respiratory tract secretions. Intensive Care Med. 2003; 29:2204-10.
13. Philips B J, Redman J, Brennan A L.*et al* Glucose in bronchial aspirates increases the risk of respiratory MRSA in intubated patients. Thorax. 2005; 60:761–64.
14. Baker EH, Janaway CH, Philips BJ, Brennan AL, Baines DL, Wood DM, Jones PW. Hyperglycaemia is associated with poor outcomes in patients admitted to hospital with acute exacerbations of chronic obstructive pulmonary disease. Thorax. 2006;61(4):284-9.
15. Barnes PJ and Celli BR. Systemic manifestations and comorbidities of COPD. Eur Respir J. 2009;33:1165-85.
16. Schulz C, Wolf K, Harth M, Krätzel K, Kunz-Schughart L, Pfeifer M. Expression and release of interleukin-8 by human bronchial epithelial cells from patients with chronic obstructive pulmonary disease, smokers, and never-smokers. Respiration. 2003 May-Jun;70(3): 254-61.
17. Mukaida N, Shiroo M, Matsushima K. Genomic structure of the human monocyte-derived neutrophil chemotactic factor IL-8. J Immunol. 1989;143(4):1366–1371
18. Baggiolini M, Loetscher P, Moser B (1995) Interleukin-8 and the chemokine family. Int J Immunopharmacol. 1995; 17:103–108
19. Schulz C, Wolf K, Harth M, Kratzel K, Kunz-Schughart L, Pfeifer M. Expression and release of interleukin-8 by human bronchial epithelial cells from patients with chronic obstructive pulmonary disease, smokers, and never smokers. Respiration. 2003;70(3):254-61.
20. Yusuf K, Ilyas M, Tabri N, Katu S, HP F, Kasim H, et all. The correlation between bacterial colonization and interleukin-8 serum levels in acute exacerbation of COPD. International Journal of Medical Reviews and Case Reports. 2019;3(11):702-706.
21. Cimini F.A., Barchetta I, Porzia A, Mainiero F, Costantino C, Bertoccini, L, et. Circulating IL-8 levels are increased in patients with type 2 diabetes and associated with worse inflammatory and cardiometabolic profile. Acta Diabetologica. 2017;54(10):961–967.
22. Halberg N, Khan T, Trujillo ME, Wernstedt-Asterholm I, Attie A; D, Sherwani S, Wang ZV, Landskroner-Eiger S, Dineen S, Magalang UJ, Brekken RA, Scherer PE. Hypoxia-inducible factor 1alpha induces fibrosis and insulin resistance in white adipose tissue. Mol Cell Biol. 2009;29(16):4467-83
23. Halberg N, Khan T, Trujillo M.E, Wernstedt-Asterholm I, Attie A.D, Sherwani S, et al. Hypoxia Inducible Factor 1 Induces Fibrosis and Insulin Resistance in White Adipose Tissue. Molecular and Cellular Biology. 2009;29(16):4467–4483

How to cite this article: Armita Dewi, Faisal Yunus, Nirwana Fitriani Walenna, Irawaty Djaharuddin, Arif Santoso, Nur Ahmad Tabri et.al. Association of chronic obstructive pulmonary disease exacerbation with type-2 diabetes mellitus comorbidity: possibility role of IL-8. *International Journal of Research and Review*. 2024; 11(10): 441-444. DOI: *https://doi.org/10.52403/ijrr.20241039*

******