Sys Rev Pharm 2020; 11(2): 342 – 346
A multifaceted review journal in the field of pharmacy
E-ISSN 0976-2779 P-ISSN 0975-8453

The Relationship between Expressions of Toll-Like Receptor 4 and BODE Index Score in Patients with Chronic Obstruction Pulmonary Disease

Ahmed Abdullah Ajrash Al-Khafaji[1], Yesar MH Al-Shamma[2], Najah R Hadi[3*], Ali M Janabi[4]
[1]AL-Merjan Hospital, Babylon Health Directorate, Babel, Iraq, E mail: aa0107279@gmail.com
[2]College of Dentistry, Islamic University, Najaf, Iraq, yesarmh47@iunajaf.edu.iq
[*3]Department of Pharmacology and Therapeutic, Faculty of Medicine, University of Kufa, Najaf, Iraq, E mails:, drnajahiraq@gmail.com
[4]Department of Pharmacology and Toxicology, Faculty of Pharmacy, University of Kufa, Najaf, Iraq, E mail: alimhjanabi@gmail.com
Corresponding Author E-mail: drnajahiraq@gmail.com

Article History: *Submitted: 06.12.2019* *Revised: 20.01.2020* *Accepted: 18.02.2020*

ABSTRACT
Chronic obstructive pulmonary disease (COPD) is a group of common medical disorders. Morbidity and mortality rate of this disease are increasing due to lack of both effective treatment and full understanding of pathogenesis and mechanism of this disease. Thus, current study aims to investigate the relationship between the expression of toll-like receptor 4 (TLR4) and BODE index in patient with COPD as a part of potential mechanism in the developing of COPD. This study is a case control study conducted in both Alsadar and Almerjan hospitals. A total of 187 individuals 87 patients with COPD and 100 people without COPD) were selected after application of inclusion and exclusion criteria. Using RT-PCR, the expression of TLR4 was investigated. FEV1/FVCratio was examined using spirometry. There was a significant decrease in the expression of TLR4 among COPD patients when compared with healthy individuals ($P < 0.001$). COPD patients showed a significant increase in BODE index when compared with control people ($P< 0.001$). The decrease in the level of TLR4 expression in association with increased BODE index might consider as a suitable indicator for stability and chronicity of the disease. The pulmonary function test is still convenient method for screening and diagnosis of COPD.

Keywords: Toll-like receptor 4, BODE index score, chronic obstruction pulmonary disease

Correspondence:
Najah R. Hadi
Faculty of Medicine, University of Kufa, Iraq
E-mail: drnajahiraq@gmail.com

DOI: 10.5530/srp.2020.2.51

INTRODUCTION

Chronic obstructive pulmonary disease (COPD) refers to a group of lung diseases characterized by air way inflammation and tissue destruction with irreversible air flow limitation. This limitation is generally progressive and associated with abnormal response of the lungs to noxious particles or gases such as cigarette smoke, coal mining dust, diesel exhaust particles and fumes from burning biomass fuels for cooking or heating and, hence, leading to chronic air way inflammation [1-2]. COPD is a major cause of illness and death globally and is estimated as the third highest cause of mortality worldwide [3]. Treatments that effectively halt progression, reverse the disease or reduce the occurrence and/or severity of exacerbation are urgently required [4]. The lack of effective treatment results largely from the incomplete understanding of the mechanism of pathogenesis of COPD. The pathogenesis of this disease is driven by chronic inhalation of noxious particles, often cigarette smoke that persistently stimulates innate and inflammatory response [5]. Toll-like receptors (TLRs) are members of the pattern recognition receptors family (PRR). They are play crucial roles in initiating innate immune responses up on stimulation. TLR responds to bacterial antigens lip polysaccharide (LPS, end toxin) that occurs in high level in tobacco. There is an enhanced expression of TLR4 [6-7]. There is conflicting evidence for the roles of TLRs whereby some studies show increased expression, whereas, other showed decreased level of expression in patients which likely due to the phenotype of cells, tissues or others [8-9]. COPD patients have increased colonization by respiratory bacteria [10] and consequently, it is possibly that this could contribute to COPD pathogenesisvialong-term stimulation of TLRs. Pulmonary Function Test (PFT) permits an accurate measurement of the respiratory function and severity level of COPD when compared with healthy person that are estimated according to the basis of height, age and race [11-13]. The assessment of COPD disease severity requires a multi-dimensional approach. Thus, this has led to development of multi-dimensional indices BODE index (Body mass index, Obstruction, Dyspnea, Exercise). The BODE index assesses disease severity by measuring body mass index, degree of airflow obstruction (FEV1% predicted), dyspnoea (Medical Research Council Dyspnoea Scale MRC), and Exercise limitation (as measured by the 6-minute walking test 6MWT).BODE index score divided into 4 quartiles; a higher BODE index score indicates a greater mortality a among COPD groups [14-16].

MATERIALS AND METHODS

Study design, settings and duration

This study was a case control study conducted in respiratory consultancy clinic of Al-Sadar Teaching Hospital at Al-Najaf governorate / Iraq and Merjan Teaching Hospital at Babylon governorate / Iraq during the period January-December 2018, sample size included87 patients with COPD and 100 healthy people. After application of demographic data and inclusion and exclusion criteria, BMI was measured, and blood samples were obtained to assess the expression of TLR4.FEV1/FVCratio was examined using spirometry.

Statistical analysis

All data are either mean ± SD or frequencies (as percentages) using SPSS, version 24. Multiple contingency tables were conducted, and appropriate statistical tests performed. Chi-square test was used for categorical variables (Fishers exact test was used when total expected variables were less than 20%). Independent sample t-test was used to compare between two means. Statistical significance was considered for P <0.05.

RESULTS

Demographic distribution of Age, gender and body mass index of study participants

There was no significant difference in mean age between COPD patients and healthy people. Moreover, no significant differences were observed between COPD patients and control people regarding their gender. Furthermore, there was no significant difference in mean BMI between COPD patients and control individuals, see table (1).

Table (1): Demographic distribution of age, gender and body mass index of study groups

Variable	COPD Mean ± SD*	Controls Mean ± SD*	P value *	OR	95% CI
Age (years)	46.5±9.48	45.1±11.4	0.38	1.6	{-1.74-4.5}
BMI	28.1±4.5	26.7±5.1	0.07	1.3	{-0.1-2.7}
Gender					
Male	75(96.2%)**	95(95%)**	0.7	1.3	{0.3 -5.6}
Female	3 (3.8%)**	5 (5 %)**			

*Independent sample t-test, OR=Odds Ratio, CI=Confidence Interval.
** Fishers exact test, OR=Odds Ratio, CI=Confidence Interval.

Spirometry findings of study groups

There was a significant decrease of FEV1/FVC ratio among COPD patients when compared with healthy people (p<0.001; OR=-33.4) (Table 2).

Table (2): Distribution of FEV1/FVC according to COPD patients and controls

Variable	COPD Mean ±	Control Mean ±	P value *	OR	95% CI
FEV1/FVC	48.7±3.6	82.4±3.04	< 0.001	-33.4	{-6.4_ -

*Independent sample t-test, FEV1=First Second of Forced Expiration, FVC=Forced Vital Capacity, OR=Odds Ratio, CI=Confidence Interval.

Expression of toll-like receptor 4

The TLR4 expression was significantly decreased in COPD patients when compared to healthy individual (p=0.001; OR=-1.6) (Table 3).

Table (3): Distribution of TLR4 according to COPD patients and controls

Variable	COPD Mean ± SD	Controls Mean ± SD	P value *	OR	95% CI
TLR4	10.3±3.8	11.9±2.8	0.001	-1.6	{-2.6_ -0.6}

*Independent sample t-test, OR=Odds Ratio, CI=Confidence Interval.

BODE index score

The BODE index score of COPD patients was classified into four quartiles; quartile 1 (0-2) was represented by 48 (55.2%) COPD patients, quartile 2 (3-4) was represented by 21 (24.1%) COPD patients, quartile 3 (5-6) was represented by 11 (12.6%) COPD patients and quartile 4 (7-10) was represented by 7 (8.1%) COPD patients, while all controls were belong quartile 1 BODE index score. There was a significant association between higher BODE index score and COPD patients (p < 0.001), table (4).

Table (4): Distribution of BODE index score according to COPD patients and controls

Variable	COPD No.	COPD %	Controls No.	Controls %	P value	OR	95% CI
BODE index score					<0.001	1.3	{0.3_5.6}
Quartile 1 (0-2)	48	55.2	100	100.0			
Quartile 2 (3-4)	21	24.1	0	-			
Quartile 3 (5-6)	11	12.6	0	-			

Quartile 4 (7-	7	8.1	0	-			

* Fishers exact test, OR=Odds Ratio, CI=Confidence Interval.

DISCUSSION

The chronic obstructive pulmonary disease is anticipated to be in the top list of death causing diseases all over the world at 2030 [17]. COPD is associated with a gradual limitation of airflow and stimulated chronic airways inflammation [18]. The inflammatory markers and classifications of severity for patients with COPD are all aimed to help physicians to predict patients at risk for early treatment in attempt to decrease the morbidity and mortality rates [19]. The prevalence of smoking in Iraq has increased in post-conflicts after 2003 and this higher rate had been attributed to political reasons, capacity building and technical reasons and law enforcement reasons [20]. Smoking in young people is strongly linked to early development of COPD and earlier co-morbidities of COPD and death [21]. Current study showed no significant difference in age between COPD patients and healthy people. This finding is essential in excluding the confounding effect of age on results of this study. It was found that the age is an important risk factor for development and severity of COPD [22]. In Iraq, because of traditions and religious restrictions, smoking of women is considered as social stigmata which fortunately reduced the behaviour of smoking among Iraqi women [23]. In the UK, a current study carried out by Peters et al (2014) reported that differences between both men and women regarding smoking behaviour had been diminished in last decades as there was a rise in smoking prevalence among women. Many researchers suggested that the risk of long duration smoking is higher among women in comparison to men. Some studies reported that the lung cancer probability was increased among women with equal smoking/packs per year as men leading to fact that smoking is riskier in women than men [24-25]. The inverse relationship between BMI and COPD is also found in other chronic diseases like type 2 diabetes mellitus [26] cerebrovascular accidents [27] and chronic renal disease [28]. Till now, this inverse relationship between mortality of COPD and BMI is controversial and dose-response relationship [29]. For normal non-smoker population, the decline in FEV1 is approximately ranging between 30-50 ml per year [30]. When the rate of decline is higher than this rate, it is regarded as an abnormal rapid decline. High suspicion was around the selection of better threshold level of forced expiratory ratio and using it for diagnosis of COPD as these forced expiratory ratios are declined with age in normal population [31]. This may lead to false positive diagnosis of normal elderly peoples as COPD [32]. Additionally, the classification of severity of COPD based on FEV1 might also be misclassifying the COPD among elderly population as misclassifying elderly patients in GOLD stage I as GOLD stage II [33], although these limitations of FEV1, all international guidelines apply forced expiratory ratio for COPD [(2)]. Present study showed low level of TLR4 among COPD patients when compared to healthy individuals. This result might be due to activity or chronicity of the disease. This is relatively in line with data conducted in a study in Netherlands which reported TLR4 level of 10.8 ng/µL among COPD patients [34], this finding is consistent with results of a study in South Korea which enrolled 53 smoker patients and found that FEV1/FCC ratio was significantly increased with the increase of TLR4 level, while emphysema score is decreased with the increase of TLR4 level [35]. Data of this study were inconsistent with results of a study conducted in India which found that gene expression of TLR2 and TLR4 were increased in lip polysaccharide-stimulated peripheral blood Neutrophils of COPD. These differences in studies are explained by a study conducted in Sweden which found that TLR2 level is decreased in sputum Neutrophils of COPD while there was no significant difference between smokers with COPD and smokers without COPD regarding TLR4 expression. They reported that TLRs are the first line of defence against invading microorganisms, but they are differently regulated in smokers with COPD compared with smokers without COPD. Nowadays, many studies found a strong association between innate immunity and COPD. Innate immunity included phagocytes of inflammatory cells that dissociate between pathogens and self-cells by using signals from TLRs. These receptors are essential in COPD, since they have an important defensive role against viral and bacterial infections, and these infections of airways will exacerbate COPD disease [37], TLR4 plays a role in lung homeostasis through participating in defensive mechanism of endothelial cells against oxidants [38]. The BODE index score of COPD patients in current study was classified into four quartiles; quartile 1 (55.2%), quartile 2 (24.1%), quartile 3 (12.6%) and quartile 4 (8.1%). These findings are in line with the results of a study which revealed that BODE index scoring of older COPD patients is precise in prediction of risks and mortality and they showed that about 50% of COPD patients were in quartile 1 [39]. Current study showed a highly significant association between higher BODE index score and COPD patients. This is in agreement to results of studies which documented that BODE index score was predominantly increased in COPD patients with high risk of mortality [40-41]. Another study found that BODE index was strongly related to health-related quality of life in patients with stable COPD and the BODE was better than Gold staging of COPD in prediction of COPD severity [42]. Thus, many researchers strongly advise the multiple applications of BODE index for evaluating health and predicting morbidity and mortality risk of COPD patients.

CONCLUSION

TLR4expression in patients with COPD is declined, implicating an important role in diagnosis of chronicity of obstructive pulmonary disease. Additionally, the BODE index is the best readout for severity assessment and mortality of COPD. Moreover, the decreased level of TLR4 in association with increased of BODE index might be considered as a good indicator for chronicity of disease. Finally, the pulmonary function test measurement of forced expiratory ratio is still easiest method for screening and diagnosis of COPD.

REFERENCES

1. Celli BR, Cote CG, Marin JM. (2004). The body-mass index, airflow obstruction, dyspnea, and exercise capacity index in chronic obstructive pulmonary disease. N Engl J Med, 350(10):1005–1012.
2. Global Initiative for Chronic Obstructive Lung Disease (GOLD). Global Strategy for the Diagnosis, Management and Prevention of COPD[2013]. Available online: http://www.goldcopd.org/
3. National institute for health and care excellence (NICE 2010), chronic pulmonary disease; management of COPD in adult in primary and secondary (partial up date) . London: National clinical Guideline centere, 2010).
4. Fricker M, Deane A, Hansbro PM. Animal models of chronic obstructive pulmonary disease. Expert opin Drug Disc 2014; 9: 629-645.
5. Keely S, Talley NJ, Hanspro PM. Pulmonary-intestinal cross-talk in mucosal inflammatory disease. Mucosal Immunol[2012]; 5: 7-18.
6. Pons J, Saulleda J, Regueiro V, et al Expression of Toll-like receptor 2 is up-regulated in monocytes from patients with chronic obstructive pulmonary disease. Respir Res [2006]; 7: 64.
7. Simpson JL, McDonald VM, Baines KJ, et al. Influence of age, past smoking, and disease severity on TLR2, neutrophilic inflammation, and MMP-9 levels in COPD. Mediators Inflamm [2013]; 2013: 462934.
8. von Scheele I, Larsson K, Dahlén B, Billing B, Skedinger M, Lantz AS, et al. (2011). Toll-like receptor expression in smokers with and without COPD. Respir Med, 105(8):1222-1230.
9. Geraghty p, Dabo AJ, D'Armiento J. TLR4 protein contributes to cigarette smoke-induced matrix met alloproteinase-I (MMP-1) expression in chronic obstructive pulmonary disease. J BiolChem[2011]; 286: 30211-30218.
10. Simpson JL Baines KJ, Horvat JC,et al. COPD is characterized by increased detection of Haemophilus influenzae, Streptococcus pneumoniae and a deficiency of Bacillus species. Respirology[2016]; 11: e0146102.
11. Marion, M.S.; Leonardson, G.R.; Rhades, E.R.; Welty, T.K; Paul, L. and Enright, P.L.(2001). Spirometry Reference values for American Indian Adults. Chest., 120:489-495.
12. Fulambarker, A.; Coper, A.S.; Javeri, A.; Jeres, S. and Cohen, M.E.(2004). Reference values for pulmonary function in Asian Indians living in the United States. Chest.,126:1225- 1233.
13. Effors, R.M. (2006). Anatomy, development, and physiology of the lungs. Nature Publishing Group.
14. Celli BR, Cote CG, Marin JM. (2004). The body-mass index, airflow obstruction, dyspnea, and exercise capacity index in chronic obstructive pulmonary disease. N Engl J Med, 350(10):1005–1012.
15. NurhanSarioglu, Aylin OzgenAlpaydin, Aysinsakercoskun, pinarcelik, Beyhancengizozyurt, ArzuYorgancioglu, Multidisciplinary respiratory Medicine 2010; 5(2): 84 – 91 .
16. Simona E. Busulac ,HmarikeBoezen , Pieter S. , Hiemstra , theresslapperre , JUDI th m. vonk , wimtimens , DIRK JE S.POSTMA .(2012) ; 7(8) : e431 24
17. Mathers CD, Loncar D. (2006). Projections of global mortality and burden of disease from 2002 to 2030. PLoS Med, 3(11):e442.
18. Qaseem A, Wilt TJ, Weinberger SE. (2011). Diagnosis and management of stable chronic obstructive pulmonary disease: a clinical practice guideline update from the American College of Physicians, American College of Chest Physicians, American Thoracic Society, and European Respiratory Society. Ann Intern Med, 155:179–191.
19. Thomsen M, Ingebrigtsen TS, Marott JL, Dahl M, Lange P, Vestbo J, et al. (2013). Inflammatory biomarkers and exacerbations in chronic obstructive pulmonary disease. JAMA, 309(22):2353-2361.
20. Hussain Z, Sullivan R. (2017). Tobacco in post-conflict settings: the case of Iraq. Ecancermedicalscience, 11: 735.
21. Jiménez-Ruiz CA, Andreas S, Lewis KE, Tonnesen P, van Schayck CP, Hajek P, et al. (2015). Statement on smoking cessation in COPD and other pulmonary diseases and in smokers with comorbidities who find it difficult to quit. Eur Respir J, 46(1):61-79.
22. Fukuchi Y. (2009). The aging lung and chronic obstructive pulmonary disease: similarity and difference. Proc Am Thorac Soc, 6(7):570-572.
23. Al-Mousawi A. (2014). The Prevalence of smoking among Karbala/Iraq University students in Iraq in 2005. Tobacco Use Insights, 7: 9–14.
24. Huxley R, Jamrozik K, Lam TH, (2007). Impact of smoking and smoking cessation on lung cancer mortality in the Asia-Pacific region. Am J Epidemiol, 165:1280–1286.
25. Feigin V, Parag V, Lawes CM, (2005). Smoking and elevated blood pressure are the most important risk factors for subarachnoid hemorrhage in the Asia-Pacific region: an overview of 26 cohorts involving 306,620 participants. Stroke, 36:1360–1365.
26. Liu XM, Liu YJ, Zhan J. (2014). Overweight, obesity and risk of all-cause and cardiovascular mortality in patients with type 2 diabetes mellitus: a dose–response meta-analysis of prospective cohort studies. Eur J Epidemiol, 30:35–45.
27. Bagheri M, Speakman JR, Shabbidar S. (2015). A dose–response meta-analysis of the impact of body mass index on stroke and all-cause mortality in stroke patients: a paradox within a paradox. Obes Rev, 16:416.23.
28. Kovesdy CP, Anderson JE, Kalantar-Zadeh K. (2007). Paradoxical association between body mass index and mortality in men with CKD not yet on dialysis. Am J Kidney Dis, 49:581–591.
29. Galesanu RG, Bernard S, Marquis K. (2014). Obesity in chronic obstructive pulmonary disease: is fatter really better? Can Resp J, 21:297–301.
30. Kerstjens HA, Rijcken B, Schouten JP, Postma DS. (1997). Decline of FEV1 by age and smoking status: facts, figures, and fallacies. Thorax, 52(9): 820-827.
31. Hankinson JL, Odencrantz JR, Fedan KB. (1999). Spirometric Reference Values from a Sample of the General U.S. Population. Am J Respir Crit Care Med, 159:179-187.

32. Vaz Fragoso CA, Concato J, McAvay G, Van Ness PH, Rochester CL, Yaggi HK, et al. (2009). The ratio of FEV1 to FVC as a basis for establishing chronic obstructive pulmonary disease. American journal of respiratory and critical care medicine, 181(5): 446-451.
33. Fragoso CA, Concato J, McAvay G, Yaggi HK, Van Ness PH, Gill TM. (2011). Staging the severity of chronic obstructive pulmonary disease in older persons based on spirometric Z-scores. Journal of the American Geriatrics Society, 59(10): 1847-1854.
34. Budulac SE, Boezen HM, Hiemstra PS, Lapperre TS, Vonk JM, Timens W, et al. (2012). Toll-like receptor (TLR2 and TLR4) polymorphisms and chronic obstructive pulmonary disease. PloS one, 7(8): e43124.
35. Lee S. W, Kim DR, Kim TJ, Paik JH, Chung JH, Jheon S, et al. (2012). The association of down-regulated toll-like receptor 4 expression with airflow limitation and emphysema in smokers. Respiratory research, 13(1): 106.
36. Tripathi PM, Kant S, Yadav RS, Kushwaha R, Prakash V, Rizvi S, et al. (2017). Expression of Toll-like Receptor 2 and 4 in Peripheral Blood Neutrophil Cells from Patients with Chronic Obstructive Pulmonary Disease. Oman medical journal, 32(6): 477-485.
37. Sarir H, Henricks PA, van Houwelingen AH, Nijkamp FP, Folkerts G. (2008). Cells, mediators and Toll-like receptors in COPD. Eur J Pharmacol, 585:346–353.
38. Maes T, Bracke KR, Vermaelen KY, Demedts IK, Joos GF, Pauwels RA, et al. (2006). Murine TLR4 is implicated in cigarette smoke-induced pulmonary inflammation. Int Arch Allergy Immunol, 141:354–368.
39. Pedone C, Scarlata S, Forastiere F, Bellia V, Antonelli Incalzi R. (2014). BODE index or geriatric multidimensional assessment for the prediction of very-long-term mortality in elderly patients with chronic obstructive pulmonary disease? a prospective cohort study. Age Ageing, 43(4):553-558.
40. Esteban C, Quintana JM, Moraza J, Aburto M, Aguirre U, Aguirregomoscorta JI, et al. (2010). BODE-Index vs HADO-score in chronic obstructive pulmonary disease: Which one to use in general practice? BMC medicine, 8: 28.
41. Cote CG, Pinto-Plata VM, Marin JM, Nekach H, Dordelly LJ, Celli BR. (2008). The modified BODE index: validation with mortality in COPD. Eur Respir J, 32(5):1269-1274.
42. Sarkar SK, Basuthakur S, Das SK, Das A, Das S, Choudhury S, et al. (2015). Evaluation of correlation of BODE index with health-related quality of life among patients with stable COPD attending a tertiary care hospital. Lung India: official organ of Indian Chest Society, 32(1): 24-28.