arly detection and diagnosis of chronic obstructive pulmonary disease in asymptomatic male smokers and ex-smokers using spirometry

La frecuencia de las cardiopatías congénitas entre los recién nacidos prematuros

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Background: Chronic obstructive pulmonary disease (COPD) has a great role for causing long-lasting morbidity of the body, also early death in addition to great cost for healthcare system. Tobacco smoking represents the

most predominant risk factor for causing this disease. The early symptoms like cough and wheeze are commonly overlooked by the patients without good screening and

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ate exertion and when they reach this time, about half of the ventilatory reserve can be lost. The use of Spirometry represents the best standard to diagnose and follow up of patients with chronic obstructive pulmonary disease. **Aim of study:** The study aimed to early detect and diagnose chronic obstructive pulmonary disease in asymptomatic male smokers and ex-smokers by spirometry.

Patients and methods: Consecutive asymptomatic male current smokers (n=100) and ex-smokers (n=100) were participated in screening. All Participants have no history of

(COPD), asthma, chronic pulmonary illness or active pulmonary symptoms. Also, all of them not on bronchodilators, inhaled corticosteroids, montelukast, or theophylline.

Results: A total of 100 asymptomatic male current smokers

and 100 asymptomatic male ex-smokers were screened by using spirometer, the procedure of using spirometer was

done according to the guidelines of American Thoracic Society and European Respiratory Society. Overall, airway

obstruction was seen in 49% current smokers, 22% of patients had mild obstruction and 27% subjects. Thirteen patients (13%) had mild obstruction while 39% cases had moderate obstruction.

Conclusions: The early detection of COPD is very important for cessation of smoking in addition to prevent the exacerbation of COPD, improve pulmonary function, life quality and reduce mortality.

Key words: Spirometry, chronic obstructive pulmonary disease (COPD).

Abstract

Antecedentes: La Enfermedad Pulmonar Obstructiva Crónica (EPOC) tiene un gran papel como causante de morbilidad duradera del organismo, también muerte prematura además de un gran costo para el sistema de salud. El tabaquismo representa el factor de riesgo más predominante para causar esta enfermedad. Los primeros síntomas como la tos y las sibilancias suelen ser pasados por alto por los pacientes sin una buena evaluación y luego tendrán disnea después de hacer un esfuerzo leve a moderado y cuando alcanzan este momento, se puede perder aproximadamente la mitad de la reserva ventilatoria. El

uso de la espirometría representa el mejor estándar para el diagnóstico y seguimiento de pacientes con enfermedad pulmonar obstructiva crónica.

Objetivo del estudio: El objetivo del estudio fue detectar y diagnosticar precozmente la enfermedad pulmonar obstructiva crónica en varones fumadores y exfumadores asintomáticos mediante espirometría.

Pacientes y métodos: Se participaron en el cribado de forma consecutiva varones asintomáticos fumadores ac-

tuales (n=100) y exfumadores (n=100). Todos los participantes no tienen antecedentes de (EPOC), asma, enfermedad pulmonar crónica o síntomas pulmonares activos. Además, todos ellos no toman broncodilatadores, corticosteroides inhalados, montelukast o teofilina.

Resultados: Un total de 100 hombres fumadores actuales asintomáticos y 100 ex fumadores masculinos asintomáticos fueron evaluados mediante espirómetro, el procedimiento de uso de espirómetro se realizó de acuerdo con las directrices de la American Thoracic Society y la European Respiratory Society. En general, la obstrucción de las vías respiratorias se observó en el 49% de los fumadores actuales, el 22% de los pacientes tenía una obstrucción leve y el 27% de los sujetos. Trece pacientes (13%) tenían obstrucción leve mientras que el 39% de los casos tenían obstrucción moderada.

Conclusiones: La detección precoz de la EPOC es muy importante para dejar de fumar además de prevenir la exacerbación de la EPOC, mejorar la función pulmonar, la calidad de vida y reducir la mortalidad.

Palabras clave: Espirometría, enfermedad pulmonar obstructiva crónica (EPOC).



hronic obstructive pulmonary disease (COPD) is a common progressive pulmonary disease that is characterized by per-

manent airways obstruction that is caused partly either by chronic bronchitis or emphysema¹.

In clinical practice, COPD is usually underdiagnosed; many studies show that more than 25-50% of patients found to have this disease accidentally after doing spirometry screening with no previous diagnosis of COPD. The recent estimates for the disease suggest that about 80 million individuals across the world have moderate to severe COPD. In 2020, the disease accounts for the third most predominant reason for death around the world^{2,3}. The most prevalent risk factor for this disease is tobacco smoking, in addition to other risk factors can be involved like air pollution, airways genetic defects like alpha-1-antitrypsin deficiency, occupational dusts and chemicals, poor nutrition, respiratory tract infections that happen during childhood4-7 as well as inflammation that had found to have a crucial role in COPD as confirmed in a recent study^{8,9}. Logically the early diagnosis for COPD is very important to prevent appearance of advanced symptoms and complications. The early diagnosis is also important in smokers who have no symptoms which may lead smoking cessation and this lastly gradually causes slowing down the loss of lung function¹⁰. Spirometric examination represents the gold standard for diagnosis of COPD and monitoring its progression. The confirmation of diagnosis occurs when the patient with airflow obstruction has a postbronchodilator FEV1 less than 0.70^{11,12}. In most patients, the diagnosis of COPD is performed by the combination of the clinical features and spirometric examination. Any case suspected to have COPD should be confirmed by using spirometric test¹³. The National Institute of Heart, Lung, and Blood recommends to use spirometry for all smoker subjects 45 years or older, especially those who have coughing, persistent sputum production, shortness of breath, or wheezing^{14,15}. The key features in spirometric examination of COPD are FEV1 and forced vital capacity (FVC)¹⁶. FEV1 is the volume of air can be forcefully expired in one second following a full inspiration¹⁷. The FVC is the maximum air volume can be exhaled after a full inspiration. COPD diagnosis is confirmed by finding a postbronchodilator FEV1/FVC ratio of less than 70% with FEV1 less than 80 percent of the predicted¹⁸⁻²⁰. The classification of COPD severity based on spirometry findings was according to the guidelines of Global Initiative for COPD. The assessment of severity of the disease has a considerable importance in determining the suitable treatment for each patient^{21,22}. This study is aimed to early detect chronic obstructive pulmonary disease in asymptomatic male smokers and ex-smokers by spirometry.

Patients and Methods

Methods

This cross-sectional study was performed at respiratory outpatient clinic in Baghdad teaching hospital from September 2018 to July 2019, the study included 200 subjects participated in our study, 100 of them were current smokers and 100 were ex-smokers. Data about (age, residence, marital status, occupational state and smoking state which include number of cigarettes per day, duration of smoking, age of beginning smoking, pack per year and duration of quitting in ex- smokers) were collected from participants and as required.

Exclusion criteria:

1.If they stopped smoking for a period less than one year according to the definition of ex-smoker³.

2.If they have bronchial asthma, COPD, or other chronic respiratory illness.

3.If they take bronchodilators, theophylline or montelukast.

4.If they have active respiratory symptoms.

Structured questionnaire consists of socio-demographic characteristics like: age groups, marital status, residence, occupational status and smoking state which include number of cigarettes per day, duration of smoking, age of starting smoking, pack per year and duration of quitting in ex-smokers. Oxygen (O_2) saturation was measured by pulse oximeter (NINO Onyx 9500). By using a commercially available spirometer, spirometric study was done. Information was taken from each subject at the beginning of

spirometry including name, age, gender, race, in addition to measurement of weight and height. The procedure was performed according to guidelines of American Thoracic Society (ATS)²³. Diagnosis of COPD depend on finding FEV1/FVC ratio less than 0.70 and FEV1% less than 80% with no change or trivial change after doing reversibility bronchodilator test. According to the result of spirometry and depending on classification of GOLD guidelines, the subjects were classified as the following ways:

- Stage (I): mild COPD FEV1 80% predicted or more
- Stage (II): moderate COPD FEV1 range from 50 to 79% predicted
- Stage (III): severe COPD FEV1 range from 30 to 49% predicted
- Stage (IV): very severe COPD FEV1 < 30% predicted or FEV 1 < 50% and chronic respiratory failure [24].

Statistical Analysis

The programme used to analyze the data was Statistical package for social sciences version 20 (SPSS 20). The means presented the continuous variables while discrete variables were presented as numbers and percentages. The difference in mean levels of two independent samples was analyzed by using T test. significance of associations between discrete variables was analyzed by using Chisquare test. Pearson's correlation coefficient was used to estimate the direction and degree of correlation between two continuous variables. Levels of significance was determined when P value <0.05.

he mean age of the participants was (45.3±11.5) years old with an age range of (20-69) years old, 29% of them was aged (30-39) years old for current smokers and a mean age of (54.2±10.4) years old with an age range (35-69) years old, 38% of them were aged (60-69) years old for ex-smokers. All of the participants underwent spirometric screening.

- 1. Distribution of male smokers and ex-smokers according to age of starting smoking: Regarding current smokers 53% of them were started smoking at (20-29) years old of age while in ex-smokers 42% of them were started smoking at (10-19) years old of age.
- 2. Distribution of male smokers and ex-smokers according to smoking history: Regarding current smokers, the mean duration of smoking was (24.7±10.2) years and a range of (3-50) years. A large proportion (34%) of them had a range of (21-30) year's duration of smoking. A large proportion of them (49%) smoked cigarettes at a range of (20-39) cigarettes per day (Figure 6). The mean pack years was (37.0±28.3) at a range of (2-150) pack years. A large proportion (35%) of them had a range of (21-40) pack years. While in ex-smokers, the mean duration of smoking was (25.3±9.2) years and a range of (10-46) years. A large proportion (38%) of them had a range of (11-20) year's duration of smoking. A large proportion of them (48%) smoked cigarettes at a range of (40-59) cigarettes per day. The mean pack years was (45.0±26.1) at a range of (10-115) pack years. A large proportion (36%) of them had a range of (21-40) pack/year.
- 3. Mean differences of variables between current smokers and ex-smokers

Table (1) shows the mean value and range of age, age of beginning smoking, duration of smoking, number of cigarettes smoked per day, and pack/year. There was significant difference in mean value between current smokers and exsmokers according to age, number of cigarettes per day and number of pack years (p value ≤ 0.05)

4: Distribution of Participants according to the results of spirometry

Table (2) shows distribution of participants according to results of spirometric tests. In current smokers (49%) had obstructive pattern (FEV1/FVC ratio <70), from those (44.9%) had mild COPD (FEV₁ ≥80) and (55.1%) had moderate COPD (FEV₁ 79-50) according to GOLD staging, about 52% of ex- smokers had obstructive pattern, from those (25%) had mild COPD and (75%) had moderate disease according to GOLD staging.

Table 1. Descriptive data for cu	urrent smokers and	l ex-smokers			
Variables		Total No.	Current Smoker	Ex- smoker	P value
	Min -Max	20-69	20-69	35-69	
Age (y)	Mean ±SD	49.8±11.8	45.3±11.5	54.2±10.4	<0.001
Ago at starting smoking (y)	Min -Max	8-43	11-33	8-43	
Age at starting smoking (y)	Mean ±SD	20.5±6.2	20.6±5.1	20.4±7.2	0.821
Duration of smoking (y)	Min -Max	3-50	3-50	10-46	
Duration of smoking (y)	Mean ±SD	25.0±9.7	24.7±10.2	25.3±9.2	0.701
Cigorotto (dou	Min -Max	6-60	6-60	10-60	
Cigarette/day	Mean ±SD	31.5±14.4	27.9±13.9	35.1±14.0	<0.001
Dacktorar	Min -Max	1.5-150	2-150	10-115	
Pack/year	Mean ±SD	41.0±27.5	37.0±28.3	45.0±26.1	0.040

Table 2. Dist	ribution of par	ticipants accor	ding to the re	sults of pulmona	ry function tes	its		
		FEV1/FVC for	Current Smoke	r		FEV1/FVC	for Ex-smoker	
	< 70% ≥ 70%				< 70%		≥ 70%	
FEV1%	N=100	100%	N=100	100%	N=100	100%	N=100	100%
≥ 80	22	44.9%	51	100.0%	13	25.0%	48	100.0%
79 – 50	27	55.1%	0	0.0%	39	75.0%	0	0.0%
< 50	0	0.0%	0	0.0%	0	0.0%	0	0.0%
P value		< 0	.001*			<	0.001	
*p value ≤ 0.0	5 is significant							

5: Correlation of spirometric results with study variables

Table (3) shows the correlation of both FEV_1 % and $FEV_1/$ FVC ratio with study variables (age, age of beginning smoking, duration of smoking, number of cigarettes per day, number of pack years and O₂ saturation). All of the variables were significantly inversely correlated to both FEV_1 % and FEV_1/FVC ratio except O₂ saturation which was directly correlated.

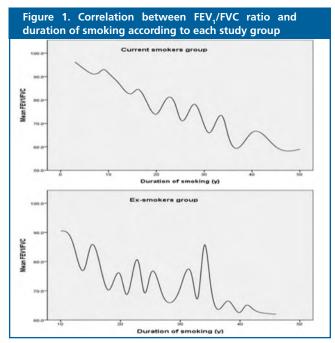
Figure)1 (illustrates the inverse correlation of FEV₁/FVC ratio with duration of smoking in the two study groups, so when duration of smoking increases, the ratio will decrease.

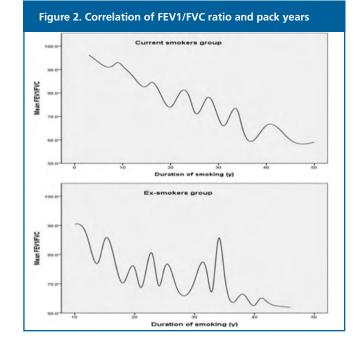
Figure (2) shows the inverse correlation of FEV₁/FVC ratio and number of pack years in the two study groups, so when number of pack years increases, the ratio will decrease.

6. Mean differences of O₂ saturation, FEV₁ % and FEV₁/ FVC ratio and between current smokers and ex-smokers Table (4) shows the mean O₂ saturation was (96.3±1.8) in current smokers and was (96.3±1.8) in ex-smokers, with a range of (93-99) in both groups. The mean FEV₁% was (82.2±6.6) in current smokers which is significantly higher than that of ex-smokers which was (79.9±7.2). The mean FEV₁/FVC ratio was (75.0±9.9) in current smokers and was (73.7±8.7) in ex-smokers.

Table 3. Correlation of FEV	% and FEV ₁ /FVC rati	io with study vari	ables			
Variables	Total		Current Smokers		Ex-smokers	
variables	r	P value	r	P-value	r	P value
	A) (Correlations of FE	/1% with study varia	bles		
Age	-0.787 [*]	< 0.001**	-0.832	< 0.001	-0.758	< 0.001
Age at starting smoking	-0.005	0.947	-0.151	0.134	0.087	0.390
Duration of smoking	-0.768	< 0.001	-0.865	< 0.001	-0.688	< 0.001
Cigarette/day	-0.794	< 0.001	-0.820	< 0.001	-0.758	< 0.001
Pack/year	-0.951	< 0.001	-0.944	< 0.001	-0.961	< 0.001
O ₂ Saturation	0.950	< 0.001	0.945	< 0.001	0.962	< 0.001
-	B) Corre	elations of FEV1/F	VC ratio with study v	ariables		
Age	-0.760	< 0.001	-0.844	< 0.001	-0.734	< 0.001
Age at starting smoking	-0.074	0.299	-0.212	0.034	0.032	0.756
Duration of smoking	-0.736	< 0.001	-0.847	< 0.001	-0.595	< 0.001
Cigarette/day	-0.741	< 0.001	-0.749	< 0.001	-0.754	< 0.001
Pack/year	-0.853	< 0.001	-0.837	< 0.001	-0.875	< 0.001
O ₂ Saturation	0.932	< 0.001	0.944	< 0.001	0.923	< 0.001

r: Pearson's correlation coefficient., negative sign means the correlation is invers, and p value ≤ 0.05 is significant





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7. Association between spirometric diagnosis and number of pack years in both study groups

Table (5) and Table (6) shows significant association between results of spirometry and number of pack years in current smokers and ex-smokers respectively, participants in both groups with a range of (21-40) pack years show obstructive pattern in spirometry.

Table 4. Mean differences of O ₂ saturation, FEV ₁ % and FEV ₁ /FVC ratio between the two study groups					
Variables		Total No	Current smokers	Ex- smokers	P-value
O coturation	Min -Max	93-99	93-99	93-99	
O_2 saturation	Mean ±SD	96.2±1.8	96.3±1.8	96.1±1.8	0.328
FEV1%	Min -Max	65-97	65-97	66-94	
FEV170	Mean ±SD	81.0±7.0	82.2±6.6	79.9±7.2	0.018 [*]
FEV1/FVC	Min -Max	55-97	59-97	55-93	
	Mean ±SD	74.4±9.3	75.0±9.9	73.7±8.7	0.335

*p value ≤ 0.05 is significant

ble 5. Association between spirometric di	agnosis and number of pack y	rears in current smokers		
Characteristics	Spirc	Dyelue		
GilaracterIStICS	Normal (%)	Obstructive (%)	P value	
Number of pack year				
< 20 pack years	33 (100%)	0 (0.00%)	<0.001*	
(21-40) pack years	19 (52.8%)	17 (47.2%)		
(41-60) pack years	0 (0.00%)	15 (100%)		
> 60 pack years	0 (0.00%)	16 (100%)		

^{*}P value ≤ 0.05 is significant

Characteristics	Spirome	Spirometric diagnosis			
	Normal (%)	Obstructive (%)	P value		
Number of pack year					
< 20 pack years	20 (100%)	0 (0.00%)			
(21-40) pack years	17 (47.2%)	19 (52.8%)	<0.001*		
(41-60) pack years	0 (0.00%)	18 (100%)			
> 60 pack years	0 (0.00%)	26 (100%)			

*P value ≤ 0.05 is significant

Discussion

hronic obstructive pulmonary disease is a highly prevalent disease that leads to high morbidity, early mortality and high expenditure for healthcare. The disease is commonly detected lately after failure of medical treatment to stop the disease progression, so, screening in order to early detect this disease is very important to for smoking cessation campaign and to reduce the bad sequel of COPD^{1,2,24,25}. In this study, we did evaluation for the results of spirometric examination of 200 asymptomatic male smokers and ex-smoker subjects. The age of study subjects was young and middle age group and this is important for the early screening of asymptomatic cases because the COPD will appear clear at elderly age group in addition to that the lung function will deteriorate gradually with increase in age, so the disease is more predominant in older age people although the highest percentage of the smoker subjects begin smoking at early period^{26, 27}. Many studies that were

done for early detection of COPD took the subjects who were above 30 years old. In our work, the prevalence of underdiagnosed airway obstruction was found in 50.5% in total sample (49.0% in current smokers and 52.0% in ex-smokers) and this was significantly related to the smoking duration and number of pack years. This finding illustrated the great importance of identifying asymptomatic smokers and ex-smokers with undetected airway obstruction. There was a significant reduction in prevalence of smokers after the national program for prevention and treatment of COPD in Finland in 2003 that led to early diagnosis for COPD in 1998 with aid of spirometry and this was followed by management in smoking cessation clinics. This gives a clue for the high benefit of the effects of early diagnosis on natural deleterious development of COPD²⁸. In a similar way, Giovino et al found that smoking cessation rate increased after early detection of airways limitation together with the increases in advice of smoking cessation²⁴. In this work, the higher percentage of airflow obstruction was because the study was performed on randomized samples that had high number of pack years in smokers and ex-smokers. Many previous studies had many various percentages and prevalence that depend on the features and criteria of the study subjects and on spirometer used in diagnosis. In a study done by Anto et al., they had found presence of airway obstruction in 18% of patients with only 4% among subjects without symptoms²⁸. In the epidemiologic study conducted by Churg et al for early detection of COPD by using spirometry, they found that airway limitation is present in about 23% of the subjects tested for detecting COPD²⁷. In a case finding study performed by Schane and colleagues in 1960 over 40 years of age using a questionnaire, physical examination and spirometry, they found that 9% of the involved subjects had airways limitation mild obstruction was found in 63.3% of smokers who had smoking history more than 20 pack years. No airways obstruction detected in those who smoke less than 20 pack years²⁹.

From this study, we conclude that use of spirometry is very useful for early diagnosis of patients with COPD and this represents a great benefit for the patient and the community. The early COPD diagnosis will enhance smoking quitting and help in prevention of COPD exacerbations, limit the rapid decline in lung function, enhance life quality and reduce mortality.

<u>References</u>

Conclusions

- Anne G. Wheaton; Yong Liu, M.J.B.C.B.V., MD2; Thomas L. Croxton, PhD, MD3; Antonello Punturieri, MD, Lisa Postow, Kurt J. GreenlundS, Chronic Obstructive Pulmonary Disease and Smoking Status — United States. Weekly. 2019. 68(24): 533–538.
- 2. US Department of Health and Human Services. Chronic obstructive pulmonary disease. Washington, D.U.D.f.s.
- Gilliland FD, B.K., McConnell R, Gauderman WJ, VoraH, Rappaport EB, Avol E, Peters JM. , Maternal smoking duringpregnancy, environmental tobacco smoke exposure and childhood lung function. Thorax. 2014;55:271–276..
- Houben JM, M.E., Ketelslegers HB, Bast A, Wouters EF, Hageman GJ. Telomere shortening in chronic obstructive pulmonary disease. Respir Med. 2009;103(2):230-6.
- Wells JM, W.G., Han Mk, Abbas N, Nath H, Mamary AJ, Regan E, Bailey WC, Martinez FJ, Westfall E, Beaty TH, Curran-Everett D, Curtis JL, Hokanson JE, Lynch DA, Make BJ, Crapo JD, Silverman EK, Bowler RP, Dranseld MT.2012. Pulmonary arterial enlargement and acute exacerbations of COPD: N ENGI J Med. 2012; 367:913-21.
- Hashim, H.O., Al-Saadi, A. H., Haider, A. H., & Zaidan, H. K. , Association of Uromodulin rs13333226 and Angiotensinogen rs699 genes variants with essential hypertension in Arab Iraqis of Babylon province. RESEARCH JOURNAL OF PHARMACEUTICAL BIOLOGICAL AND

CHEMICAL SCIENCES.2015;6(6):589-601.

- Hashim, H.O., Mohammed, M. K., Mousa, M. J., Abdulameer, H. H., Alhassnawi, A. T., Hassan, S. A., & Al-Shuhaib, M. B. S. (). Infection with different strains of SARS-CoV-2 in patients with COVID-19. Archives of Biological Sciences.2020;72(4):575-585.
- Qasim J., H.S., Ghada H., Hayder AA. AL-Hindy, High-Sensitivity Creactive protein Assessment in Bronchial Asthma: Impact of Exhaled Nitric Oxide and Body Mass Index. Systematic Reveiw in Pharmacy, 2020. 11(33):705-711.
- Amjed H., A.-H.H.A., Shahlaa Kh., Mazin J., Conicity index as an Anthropometric Index of Central Obesity in the Prediction of Adult Bronchial Asthma; Correlation with Fractional Exhaled Nitrous Oxide Tests. Medico- Legal Update.2021;21(2).
- Hodge S, H.G., Jersmann H, Matthews G, Ahern J, Holmes M, et al. Azithromycin improves macrophage phagocytic function and expression of mannose receptor in chronic obstructive pulmonary disease. Am J Respir Crit Care Med. 2008 Jul 15. 178(2):139-48.
- Eisner MD, B.J., Katz PP, Trupin L, Yelin EH, Blanc PD. (2017). Lifetime environmental tobacco smoke exposure and the risk ofchronic obstructive pulmonary disease. Environ Health.4(7):75.
- 12. Chilosi M, P.V.R.A.T.p.o.C.a.I.d.h.o.t.s.d.R.R.
- Hurst JR, V.J., Anzueto A, Locantore N, Mullerova H, Tal-Singer R, et al. Susceptibility to exacerbation in chronic obstructive pulmonary disease. N Engl J Med. 2010 Sep 16. 363(12):1128-38.
- L., B., COPD linked to cognitive impairment and memory loss. Medscape Medical News. 2013.
- Mannino DM, D.-G.E.P.J., A new approach to classication of disease severity and progression of COPD. CHEST. 2013;144(4):1179-1185.
- Gensch E, G.M., Sucher A, Li DZ, Gebremichael A, Lem-jabbar H, Mengistab A, Dasari V, Hotchkiss J, Harkema J,Basbaum C. Tobacco smoke control of mucin production in lungcells requires oxygen radicals AP-1 and JNK. J Biol Chem. 2004;279:39085–39093.
- Abbas AH., H.S., Chabuk Shahlaa Kh., Fractional Exhaled Nitric Oxide (FeNO) As Physiological Marker for Diagnosis and Follow up Asthma in Comparison with Spirometric Parameters. Indian Journal of Public Health Research & Development. 2018;9(10):903-907.
- West, R.a.S., Saul. Fast Facts: Smoking Cessation. Health Press Ltd. 2007;p. 28. ISBN 978-1-903734-98-8.
- Golpon HA, F.V., Taraseviciene-Stewart L, ScerbaviciusR, Sauer C, Welte T, Henson PM, Voelkel NF. Life after corpseengulfment: phagocytosis of apoptotic cells leads to VEGF secre-tion and cell growth. FASEB J.2004;18:1716 –1718.
- P, H.M.S., Getting beyond "now is not a good time to quit smoking": increasing motiva-tion to stop smoking. Smoking Cessation Rounds. Available from: <u>http://ottawamodel.ottawaheart.ca/sites/ottawamodel.ottawaheart.ca/les/omsc/docs/3.increasingmotivationto-stopsmoking.pdf</u> (accessed on 14 June 2015). 2007.
- Finkelstein R, F.R., Ghezzo H, Cosio MG. Alveolar in-flammation and its relation to emphysema in smokers. Am J RespirCrit Care Med.1995;152:1666 –1672.
- 22. Rycroft CE, Lanza L HA, Becker K. Epidemiology of chronic obstructive pulmonary dis-ease: a literature review. International Journal of COPD.2012;7:457-494.
- 23. Wigand, J.S.J.A., CIGARETTE DESIGN and TOBACCO PRODUCT REG-ULATION" (PDF). Mt. Pleasant, MI 48804: Jeffrey Wigand. Retrieved 2009-02-14.

- Giovino, G.M., SA; Samet, JM; Gupta, PC; Jarvis, MJ; Bhala, N; Peto, R; Zatonski, W; Hsia, J; Morton, J; Palipudi, KM; Asma, S; GATS Collaborative, Group (Aug 18, 2012). "Tobacco use in 3 billion individuals from 16 countries: an analysis of nationally representative cross-sectional household surveys." Lancet 380 (9842): 668–79.
- 25. Global Initiative for Chronic Obstructive Lung Disease (GOLD). Global strategy for the diagnosis, m., and prevention of chronic obstructive pulmonary disease (updated 2015). Avail-able from: <u>http://www.gold-copd.org/guidelines-global-strategy-for-diagnosis-management.html</u> (accessed on 15 June 2015).
- Churg A, W.R., Tai H, Wang XS, Xie CS, Wright JL. (2004). Tumornecrosis factor-alpha drives 70% of cigarette smoke-induced em-physema in the mouse. Am J Respir Crit Care Med. 170: 492–498,.
- The World Health Organization, a.t.I.f.G.T.C., Johns Hopkins School of Public Health (2001). "Women and the Tobacco Epidemic: Challenges for the 21st Century" (PDF). World Health Organization. pp. 5–6. Retrieved 2009-01-02.
- Anto RJ, M.A., Shishodia S, Gairola CG, Aggar-wal BB, Cigarette smoke condensate activates nuclear transcrip-tion factor-kappa B through phosphorylation and degradation of Ikappa B alpha: correlation with induction of cyclooxygenase-2.Carcinogenesis. 2002;23:1511–1518.
- 29. Schane RE, Ling PM, Glantz SA. Health effects of light and intermittent smoking: A review. Circulation.2010;121(13):1518-22.

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