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Annals of Clinical Pathology

Review Article

Silicosis: Pathogenesis and Biomarkers

Attapon Cheepsattayakorn[1,2]* and Ruangrong Cheepsattayakorn[3]

[1]*10 Zonal Tuberculosis and Chest Disease Center, Chiang Mai, Thailand*

[2]*Department of Disease Control, Ministry of Public Health, Thailand*

[3]*Department of Pathology, Faculty of Medicine, Chiang Mai University, Chiang Mai, Thailand*

***Corresponding author**

Attapon Cheepsattayakorn, 10th Zonal Tuberculosis and Chest Disease Center, 143 Sridornchai Road Changklan Muang Chiang Mai 50100 Thailand; Tel: 66 53 276364; Fax: 66 53 273590; E-mail: Attapon1958@gmail.com

Submitted: 04 October 2018

Accepted: 31 October 2018

Published: 31 October 2018

ISSN: 2373-9282

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OPEN ACCESS

Keywords

- Silicosis
- Biomarkers
- Pathogenesis

Abstract

Ramazzini first described this disease, namely "Pneumonoultramicroscopicsilicovolcanokoniosis" and then was changed according to the types of exposed dust. No reliable figures on the silica-inhalation exposed individuals are officially documented. How silica particles stimulate pulmonary response and the exact path physiology of silicosis are still not known and urgently require further research. Nevertheless, many researchers hypothesized that pulmonary alveolar macrophages play a major role by secreting fibroblast-stimulating factor and re-ingesting these ingested silica particles by the pulmonary alveolar macrophage with progressive magnification. Finally, ending up of the death of the pulmonary alveolar macrophages and the development of pulmonary fibrosis appear. Various mediators, such as CTGF, FBRS, FGF2/bFGF, and TNFα play a major role in the development of silica-induced pulmonary fibrosis. A hypothesis of silicosis-associated abnormal immunoglobulins has been postulated. In conclusion, novel studies on pathogenesis and biomarkers of silicosis are urgently needed for precise prevention and control of this silently threaten disease of the world.

ABBREVIATIONS

ACE: Angiotensin Converting Enzyme; ANCA: Anti-Neutrophil Cytoplasmic Antibody; ANF: Anti-Nuclear Antibody; BAL Bronchoalveolar Lavage; CSF Colony-Stimulating Factor; DCs: Dendritic Cells; DNA: Deoxyribonucleic Acid; FasL: Fas Ligand; FEV1: Forced Expiratory Volume in one second; FGF Fibroblast Growth Factor; FSF: Fibroblast-Stimulating Factor; IL: Interleukin; L-BAL: Bronchoalveolar Lavage Lymphocyte; mRNA messenger Ribonucleic Acid; MIP: Macrophage Inflammatory Protein; MCP: Monocyte Chemotactic Factor; NALP3: (or NLRP3) Nucleotide-binding oligomerization domain-Like Receptor containing Pyrin domain 3; RA: Receptor Antagonist; RF: Rheumatoid Factor; SSc: Systemic Sclerosis; SLE: Systemic Lupus Erythematosus; Th 17: T helper 17; TNF: Tumor Necrosis Factor; VC: Vital Capacity; WNT: Wingless Type

OBJECTIVE OF THE STUDY

The objective of this study is to review the new ideas of pathogenesis of silicosis and possibly practical novel biomarkers for silicosis.

INTRODUCTION

The name of this disease "Pneumonoultramicroscopicsilicovolcanokoniosis ", first description by Ramazzini [1] was changed due to the types of exposed dust [2]. There are no reliable figures on the silica-inhalation exposed populations. Nevertheless, in 2000, the CAREX registry recorded 3.2 million silica-exposed people in the European Union [3]. Silicosis is histologically characterized by hyalinized and fibrotic pulmonary nodules, accumulation of lymphocytes and alveolar macrophages, and thickening of pulmonary alveolar interstitium [4]. The diseaseis caused by continuous inhalation of the silica dust (crystalline silica, SiO_2 (Silicon dioxide)) with marked inflammation and irreversible scarring of the lungs with nodules in the upper lobes [5,6] Oxygen and silicon, together amount for 74.32 % weight and 83.77 % of crustal rocks are the two most occurring common elements on the surface of the earth [7]. Silicon dioxide or silica is formed under the conditions of increased pressure and heat that exists in amorphous and crystalline (quartz, a typical component of rocks) form. The risk of developing silicosis is closely associated with the accumulated exposure of a person to respirable crystalline silica during his or her working lifetime. The intensity of accumulated respirable silica exposure can be calculated as the following Accumulated silica dose = fraction of respirable dust X percentage of free silica in mg/m^3 X number of years of exposure [8]. Silicosis is the most frequently occurring pneumoconiosis due to wide prevalence in the atmosphere and more common than the other types of dust [1,9,10]. Both in Developing and developed world, silicosis is an occupational hazard with greater risk for workers engaged in stone crushing, stone cutting, cement industries, glass manufacturing, mining, agriculture, and construction.

PATHOGENESIS

When the silica particles of 0.5 to 5 microns in diameter are inspired into the lungs, these particles get embedded into the alveolar sacs and ducts and cause inflammation. The inflammation and scarring damage the pulmonary alveolar sacs, prevent gas

exchange in the lungs, and contribute to abnormal breathing. The damage to the lung tissue leads to reduction of oxygen supply to the blood. Silicosis isan irreversible medical condition without cure. Degree of silica-dust exposure is directly associated with occurrence of silicosis. Through the process of inhalation, different size of the silica particles deposit in the different parts of the human respiratory system. For examples, 10-5 microns in size particles reach up to upper respiratory tract causing rhinitis and laryngitis, 5-3 microns in size particles reach up to the mid-respiratory system and may cause tracheaitis, bronchitis and bronchiolitis, and 3-1 microns in size particles directly are deposited in the alveoli causing asthma, chronic obstructive pulmonary disease, and other pulmonary interstitial diseases including silicosis [11]. How silica particlesstimulate pulmonary response and the precise pathophysiology of silicosis are still research questions. Nevertheless, several studies indicated interactions between respirable silica particles and pulmonary alveolar macrophages and this interaction plays major role in the development of the silicosis disease. The intensity of the inhaled silica particles influence on the nature and extent of the pulmonary alveolar response that provides explanation to some silicosis extension why rock drillers and sandblasters who are intensively exposed to freshy fractured silica dust develop silicosis disease [12].

Several studies revealed that silica promote macrophage activation. The affected macrophages release inflammatory mediators and chemotactic factors that trigger cellular responses of the leukocytes and lymphocytes and then release the fibroblast stimulating factor (Figure 1). Hyalinization and collagen deposition are promoted by the fibroblast stimulating factor (FSF) and resulting in activation of fibroblast [13] and pathologically pulmonary nodular lesion.This pulmonary nodule composes of a central acellular zone with free silica and surrounding spirals of collagen and fibroblasts [14]. After ingestion of silica particles, pulmonary alveolar macrophages secrete fibroblast-stimulating factor. Then macrophages die due to the toxicity of the ingested silica and these silica particles are re-ingested by macrophages and this process is progressively magnified. Lysosomal enzymes are then released rapidly into the cytosol and contributing breakdown of the intracellular organelles with irreversible injury to the affected pulmonary alveolar cells. Intracellular lysosomal rupture circumstantially results in cell death. It seems that damage of the plasma membrane results in macrophage death. Nevertheless, pathogenesis of silicosis may be associated with immunological mechanism due to identification of abnormal serum immunoglobulins and immunoglobulins in the silicotic nodules

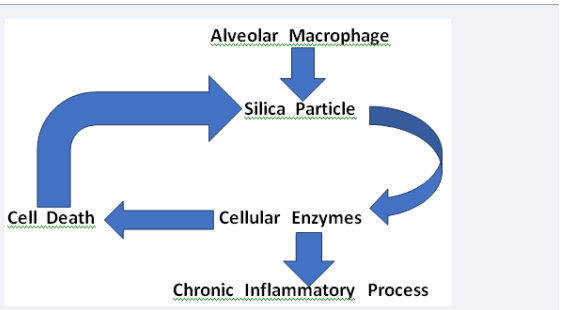

Figure 1 Impact of silica particle on pulmonary tissues.
Source: Elcosh-Electronic Library, 2016

[12]. NALP3 (or NLRP3) inflammasome-driven IL-1β mediates the inflammatory response following exposurte to crystalline silica [15]. Following uptake of silica by scavenger receptors, release of cathepsin B with production of reactive oxygen species (ROS), potassium effux, and lysosomal rupture, the activation of inflammasome occur [15-18]. Castro *et al* demonstrated in their study results that anti-deoxyribonucleic acid (anti-DNA), antimitochondrial antibody, antinuclear factor (ANF), anti-smooth muscle antibody, antithyroglobulin antibody, rheumatoid factor (RF) or latex agglutination test, thyroid antimicrosomal antibody, and Waaler-Rose test revealed the percentages of positive in the studied subjects of 20.6 %, 1.7 %, 20.6 %, 1.7 %, 1.7 %, 3.4 %, 3.4 %, and 3.4 %, respectively [19]. Early pulmonary lesions are microscopically characterized by aggregation of dust-laden macrophages that surround a collagenous central region to develop nodular to stellate lesions [20]. Then the central collagen distinctly becomes whorled and reveals decreasing number of inflammatory cells around the periphery [20]. The pulmonary nodules, called " mixed dust pneumoconiosis " that caused by a combination of silica plus another dust are likely to persist their stellate feature with less whorled arrangement in ordinary silicosis [20]. Silica particle, particularly crystalline silica or cristobalite can enhance the immune response, trigger, promote, or accelerate the development of autoimmune diseases [13,21]. According to inability to break down the crystalline silica particles by lysozymal enzymes and damaging silica-particle-ingested pulmonary alveolar macrophages with its repeated process, this phenomenon results in spreading immune activity and pulmonary fibrosis [13]. Nevertheless, recent studies have demonstrated that crystallinity does not indicate the mechanisms of silica pathogenicity, whereas silanols play the major role [22]. Many silica-exposed patients with altered immune functions are likely to develop autoimmune disorders and pulmonary fibrosis [23]. Nevertheless, approximately 20 % to 25 % of patients with silicosis and pulmonary fibrosis demonstrate better immunological status, whereas some patients reveal accelerated immunological deterioration with very slow progression of pulmonary fibrosis [23]. Dendritic cells (DCs) including T helper 17 (Th 17) cells and pulmonary alveolar macrophages play a role in pulmonary inflammation and the development of pulmonary fibrosis via signaling molecules and specific receptor although the role of DCs and Th 17 cells in the dysregulation of immune tolerance in patients with silicosis is poorly understood [24]. TNFα and the TNFR signaling pathway principal mediators in the development of silica-induced pulmonary fibrosis [25]. Silica exposure can promote the production of several fibrogenic mediators that are potentially linked indirectly to fibroblast proliferation, such as CTGF, FBRS, FGF2, proliferation and recruitment of fibroblasts, and protease to repair the pulmonary damage [25]. These fibrogenic factors may have a major impact on the intense fibrogenicity of silica [25].Silica exposure also promotes downstream signaling molecules related to the fibrogenic pathway, particularly, secretion of FGF2/bFGF and silica specifically induced mRNA levels [25]. Silica induces increased expression of TNFSF9 (CD137L/4-1BB) which is a key factor in the development of immune responses in macrophages, dendritic cells, NK cells, and T-cells, including expression in non-immune cells [25]. In silica-induced chronic inflammation, type I interferon responses play a role [25]. Nevertheless, the mechanisms of silica-induced inflammation are not well understood [25].Wingless type (WNT) signaling is not associated

with silica or silicosis although WNTsignaling is associated with the development of fibrosis [25]. Several epidemiological studies on patients with silicosis demonstrated complicated autoimmune diseases, such as anti-neutrophil cytoplasmic antibody (ANCA)-related vasculitis/nephritis [26-28], systemic sclerosis (SSc) [29-31], and systemic lupus erythematosus (SLE) [32-34]. Silica can act as a immunological trigger that required for granuloma formation in sarcoidosis [13]. Oligoclonal T cell expansion driven by an antigenic stimulus involves in pathogenesis of sarcoidosis [13]. Thus, silicosis and sarcoidosis can co-exist in the same patient [13,21]. Nevertheless, silicotic nodule with refractile particles is characteristic in silicosis, whereas presence of inclusion bodies like the asteroid bodies in noncaseating granulomas is typical in sarcoidosis [13].

BIOMARKERS

In the development of silicosis, the pulmonary alveolar macrophages play a dominant role by releasing host mediators, such as chemokines and cytokines that result in the onset of pulmonary injury, inflammation, and potentially pulmonary fibrosis. These mediators regulate the development immune effector cells. In a murine study, cristobalite-induced macrophage inflammatory protein (MIP)-2 messenger ribonucleic acid (mRNA) level were reduced by 57, 52, and 38 % with N-acetyl-L-cysteine, dimethyl sulfoxide, or extracellular glutathione, respectively [35]. Reduction of both MIP-1alpha and MIP-1beta mRNA levels were at the same magnitude as the reduction of tumor necrosis factor (TNF)-alpha mRNA levels, while MIP-2 mRNA levels were reduced at a magnitude similar to the reduction of monocyte chemotactic protein (MCP)-1 mRNA levels after antioxidant treatment [35]. Increased TNF-alpha, interleukin (IL)-1beta, IL-6, IL-8 levels were identified in bronchoalveolar lavage (BAL) fluid in patients with silicosis [36], whereas decreased cristobalite-induced TNF-alpha mRNA levels were found in a murine study [35]. A previous study revealed that soluble TNFR1 and soluble TNFR2 were increased in subjects with silica-induced pulmonary fibrosis [25]. Both canonical and non-canonical NFkB signaling drive silica-induced pulmonary inflammation and fibrosis by up-regulation of NFKB2 (p52/p100)[25]. Upregulation of the adaptor protein (TRAF1) is essential in dictating TNF-signaling via cascades including NFk3 and MAPK [25]. Human IL1 family consist of three genes located on long arm of chromosome 2 that code for IL1-a, IL1-b, and IL1 receptor antagonist (RA) [37].

Several studies revealed that serum angiotensin converting enzyme (ACE) levels were elevated in granulomatous diseases, such as silicosis and sarcoidosis [38]. Because of its principal localization in the large capillary bed of the lungs, the serum activity of ACE in pulmonary diseases is of much interest. Elevation of serum copper or ceruloplasmin could be possible associated with primary pathologic changes including fibrosis and the proliferation of collagen tissue in the lungs of patients with silicosis [39,40].In silica dust-exposed persons without developing the disease, the serum copper levels as biomarker is uncertain [41]. A experimental study in rats demonstrated a decrease in FAS-L expression and silica-induced apoptosis in old macrophages [42], whereas a study in 11 patients with silicosis revealed that bronchoalveolar lavage lymphocytes (L-BAL) apoptosis was inversely correlated with FEV1/VC value ($r = -0.26$, $p < 0.05$)[43]. Dysregulation of apoptosis in the Fas/FasL pathway play a role in the pathogenesis of autoimmune diseases [44].

DISCUSSION

Respirable silica particles with 3-1 microns in diameter are directly deposited in the pulmonary alveoli [11] and interact with pulmonary alveolar macrophages causing the silicosis disease [12]. The nature and extent of the lung response depend on the intensity of inspired silica particles [12]. Silica particlesthat deposit in the pulmonary alveoli promote pulmonary alveolar macrophage activation by releasing several chemotactic factors and inflammatory mediators. These factors and mediators, such as colony-stimulating factors (CSF), C-X-C, and C-C motif chemokinescause releasing of the fibroblast stimulating factor via the cellular response of the lymphocytes and leukocytes. Fibroblast-stimulating factor promote collagen deposition and hyalinization in the pulmonary tissues resulting in pulmonary nodule that composes of a central acellular zone with containing free silica [14]. Crystalline silica-laden macrophages cause cell death, fibrous proliferation, and finally pulmonary fibrosis. Pulmonary fibrosis is progressively magnified by re-ingestion of silica particles by macrophages. However, pathogenesis of silicosis may due to abnormal immunological mechanism [12]. Several prospectbiomarkers, such as MIP-1beta mRNA, MIP-2 mRNA, MCP-1 mRNA, TNF-alpha mRNA, IL1A, IL1B, CSF1, CSF2, IL-1beta, IL-6, IL-8, ACE could be the prognostic indicators for silicosis [25,34-37].

CONCLUSION

Further studies are urgently needed to identify suitable biomarkers for silicosis, including associated mechanism of immunoglobulins.

ACKNOWLEDGEMENTS

Dr. Attapon Cheepsattayakorn was responsible for manuscript writing. Associate Professor Dr. Ruangrong was responsible for literature search. Both author and co-author reviewed and approved the final form of the manuscript before submitting.

REFERENCES

1. Elmes PC. Inorganic dusts. In: Raffle PA, Adams PH, Baxter PJ, Lee WR, editors. Hunter's Diseases of Occupations. 9th edn. London: Edward Arnold Publications.1994; 421-428.
2. Marble Institute of America. History of silicosis. In: Silicosis, an industry guide to awareness and prevention; 2008; 3. Ohio: MIA.
3. Kogevinas. Sistema deinformacio´nsobreexposicio´noccupacional a cancerigenosen Españaen el 2004 CAREX-ESP. Barcelona: Instituto Municipal de Investigacio´nMe´dica. 2006. Available from: http://www.istas.net/web/abreenlace.asp?idenlace
4. Weill H, Jones RN, Parkes WR. Silicosis and related diseases. In: Parks WR, editor. Occupational Lung Disorders, 3rd edn. Oxford: Butterworth-Heinemann. 1994; 285-339.
5. World Health Organization. Elimination of silicosis. The Global Occupational Health Network. 2007; 1-18.
6. Greenberg MI, Waksman J, Curtis J. Silicosis: A review. Disease-a-Month. 2007; 53: 394-416.
7. Heaney PJ, Prewitt CT, Gibbs GV. Silica: physical behavior, geochemistry, and materials applications. In: Review in minerology. USA: Princeton. 1994; 29.
8. A´lvarez RF, Gonza´lez CM, Marti´nez AQ, Pe´rez JJB, Ferna´ndez LC,Ferna´ndez AP. Guidelines for the diagnosis and monitoring of silicosis. Arch Bronconeumol. 2015; 51: 86-93.

9. Mittle RE, Welti CV. The fatal cafe′ coronary. Foreign-Body Airway Obstruction. JAMA. 1982; 247: 1285-1288.

10. Broman SS, Gaissert HA. Upper airway obstruction. In: Alfrred P Fishman. Editor. Fishman's Pulmonary Diseases and Disorders. 3rd edn. New york: McGraw Hill. 1998; 785-786.

11. Community Medicine. Pneumoconiosis-ttpes, silicosis, asbestosis and preventive measures. 2015.

12. Shamin M, Alharbi WDM, Pasha TS, Nour MOM. Silicosis, a monumental occupational health crisis in Rajasthan-an epidemiological survey. Int J Res. 2017; 5: 554-583.

13. Tousheed S, Sen T, Kumar H, Bv M. Silicosis and sarcoidosis: a rare association. Chest. 2014 ; 146: 421A.

14. Shishodiya PK, Nandi SS, Dhatrak SV. Detection of silicosis among stone mine workers from Karauli district, National Institute of Miners' Health (Ministry of Miners, Government of India) jnarddc campus, Amravati road, Wadi, Nagpur report-ii. Nagpur: National Institute of Miners' Health, Government of India. 2014.

15. Cassel LS, Eisenbarth SC, Iyer SS, Sadler JJ, Colegio OR, Tephly LA, et al. The NALP3 inflammasome is essential for the development of silicosis. PNAS. 2008 ; 105 : 9035-9040

16. Hari A, Zhang Y, Tu Z, Detampel P, Stenner M, Ganguly A, et al. Activation of NLRP3 inflammasome by crystalline structures via cell surface contact. Sci Rep. 2014; 4: 7281.

17. Hornung V, Bauernfeind F, Halle A, Samstad EO, Kono H, Rock KL, et al. Silica crystals and aluminum salts activate the NALP3 inflammasome through phagosomal destabilization. Nat Immunol. 2008; 9: 847-856.

18. Leung CC, Yu IT, Chen W. Silicosis. Lancet. 2012; 379: 2008-2018.

19. Castro HAD, Silva CGD, Lemle A. Immunoglobulins, complements and auto antibodies in 58 workers exposed to silica. J Bras Pneumol. 2004.

20. Gibbs AR, Wagner JC. Diseases due to silica. In: Churg A and Green FHY, editors. Pathology of Occupational Lung Diseases. United Stated: Igaku-Shoin Medical Publishers. 1998; 155-176.

21. RafnssonV,Ingimarsson O, Hjalmarsson I, Gunnarsdottir H. Association between exposure to crystalline silica and risk of sarcoidosis. Occup Environ Med. 1998; 55: 657-660.

22. Pavan C, Fubini B. Unveiling the variability of "Guartz Hazard" in light of recent toxicological findings. Chem Res Toxicol. 2017; 30: 469-485.

23. Ocsuki T, Ichihara K, Tomokuni A, Sakaguchi H, Aikoh T, Matsuki T, et al. Evaluation of cases with silicosis using the parameters related to Fas-mediated apoptosis. Int J Mol Med. 1999; 4: 407-411.

24. Matsuzaki H, Hayashi H, Lee S, Kumagai-Takei N, Yamamoto S, Ikeda M, et al. Alteration of immune cells in silicosis: roles in development of autoimmunity and lung fibrosis. Ann Mens Health Wellness. 2017; 1: 1002.

25. Perkins TN, Peeters PM, Shukla A, Arijs I, Dragon J, Wouters EFM, et al. Indications for distinct pathogenic mechanisms of asbestos and silica through gene expression profiling of the response of lung epithelial cells. Human Mol Gen. 2015; 24: 1374-1389.

26. Wichmann I, Sanchez-Roman J, Morales J, Castillo MJ, Ocaña C, Nuñez-Roldan A. Antimyeloperoxidase antibodies in individuals with occupational exposure to silica. Ann Rheum Dis. 1996; 55: 205-207.

27. Bartunkova′ J, Pelclova′ D, Fenclova′ Z, Sediva′ A, Lebedova′ J, Tesar V, et al. Exposure to silica and risk of ANCA-associated vasculitis. Am J Ind Med. 2006; 49: 569-576.

28. Mulloy KB, Silica exposure and systemic vasculitis. Environ Health Perspect. 2003; 111: 1933-1938.

29. Sluis-Cremer GK, Hessel PA, Nizdo EH, Churchill AR, Zeiss EA, Silica, silicosis and progressive systemic sclerosis. Br J Ind Med. 1985; 42: 838-843.

30. Cowei RL. Silica-dust-exposed mine workers with scleroderma (systemic sclerosis). Chest. 1987; 92: 260-262.

31. Haustein UF, Ziegler V, Herrmann K, Mehlhorn J, Schmidt C. Silica-induced scleroderma. J Am Acad Dermatol. 1990; 22: 444-448.

32. Lucas CD, Amft N, Reid PT. Systemic lupus erythematosus complicating simple silicosis. Occup Med (Lond). 2014; 64: 387-390.

33. Sanchez-Roman J, Wichmann I, Salaberri J, Varela JM, Nuñez-Roldan A. Multiple clinical and biological autoimmune manifestations in 50 workers after occupational exposure to silica. Ann Rheu Dis. 1993; 52: 534-538.

34. Koeger AC, Lang T, Alcaix D, Milleron B, Rozenberg S, Chaibi P, et al. Silica-associated connective tissue disease: a study of 24 cases. Medicine (Baltimore). 1995; 74: 221-237.

35. Barrett EG, Johnston C, Oberdorster G, Finkelstein JN. Antioxidant treatment attenuates cytokine and chemokine levels in murine macrophages following silica exposure. Toxicol Appl Pharmacol. 1999; 158: 211-220.

36. Zhai R, Ge X, Li H, Tang Z, Liao R, Kleinjans J. Differences in cellular and inflammatory cytokine profiles in the brochoalveolar lavage fluid in bagassosis and silicosis. Am J Ind Med. 2004; 46: 338-344.

37. Tiwari RR. Biomarkers of silicosis: potential candidates. Indian J Occup Environ Med. 2005; 9: 103-106.

38. Lieberman J. Elevation of serum angiotensin-converting-enzyme (ACE) level in sarcoidosis. Am J Med. 1975; 59: 365-372.

39. Wang W, Wang L, Yiwen L. Serum concentrations of copper and zinc in patients with silicosis. J Occup Health. 1998; 40: 230-231.

40. Niculescu T, Dumitru R, Burnea D. Changes of copper, iron and zinc in the serum of patients with silicosis, silico-tuberculosis and active lung tuberculosis. Environ Res. 1981; 25: 260-268.

41. Tiwari RR, Sathwara NG, Saiyed HN. Silica exposure and serum copper: a cross-sectional study. Indian J PhysiolPharmacol. 2004; 48: 337-342.

42. Corsini E, Giani A, Lucchi L, Peano S, Viviani B, Galli CL, et al. Resistance to acute silicosis in senescent rats: role of alveolar macrophages. Chem Res Toxicol. 2003; 16: 1520-1527.

43. Szczeklik J, Trojan J, Kopinski P, Soja J, Szlubowski A, Dziedzina S, et al. Apoptosis of bronchoalveolar lavage lymphocytes (L-BAL) in pneumoconiosis. Przegl Lek. 2004; 61: 235-240.

44. Nagata S. Fas ligand-induced apoptosis. Annu Rev Genet. 1999; 33: 29-55.

Cite this article

Cheepsattayakorn A, Cheepsattayakorn R (2018) Silicosis: Pathogenesis and Biomarkers. Ann Clin Pathol 6(5): 1147.