JBACHS
Journal of Basic and Clinical Health Sciences

J Basic Clin Health Sci 2023; 7: 529-536
https://doi.org/10.30621/jbachs.1070489
REVIEW ARTICLE

HISTOPATHOLOGICAL CHANGES IN LUNG TISSUE CAUSED BY DIABETES: A REVIEW

Aysegul Burcin Yildirim[1], Derya Karabulut[2], Emin Kaymak[3], Nurhan Kuloglu[4], Ali Tugrul Akin[5], Tayfun Ceylan[6], Emel Ozturk[7]

[1] Gaziantep Islam Science and Technology University, Faculty of Medicine, Department of Histology and Embryology, Gaziantep, Turkey
[2] Erciyes University, Faculty of Medicine, Department of Histology and Embryology, Kayseri, Turkey
[3]Yozgat Bozok University, Faculty of Medicine, Department of Histology and Embryology, Yozgat, Turkey.
[4]Niğde Ömer Halisdemir University, Niğde Zübeyde Hanım Vocational School of Health Services, Health Care Services, Niğde, Turkey
[5]Erciyes University, Faculty of Science, Department of Biology, Erciyes University, Kayseri, Turkey
[6]Cappadocia University, Cappadocia Vocational School, Department of Medical Services and Tecnigue, Pathology Laboratory Techniques, Nevşehir, Turkey.
[7]Harran University, Faculty of Medicine, Department of Histology and Embryology, Şanlıurfa, Turkey.

ORCID: A.B.Y. 0000-0001-7240-9997, D.K. 0000-0003-2067-6174, E.K. 0000-0002-3818-2693, N.K. 0000-0002-1199-2784, A.T.A. 0000-0002-1408-8571, T.C. 0000-0002-0917-0378, E.O. 0000-0003-0756-0329

Corresponding author: Ayşegül Burçin Yildirim, **E-mail:** aysegulburcin@gmail.com
Received: 15.02.2022; **Accepted:** 13.08.2022; **Available Online Date:** 31.01.2023

Cite this article as: Yildirim AB. Karabulut D. Kaymak E. Kuloglu N. Akin AT. Ceylan T. Ozturk E. Histopathological Changes In Lung Tissue Caused By Diabetes: A Review. J Basic Clin Health Sci 2023; 7: 529-536.

ABSTRACT

Diabetes mellitus (DM) associated with oxidative stress and inflammation can affect many organs. While the effects of diabetes on many organs are well known and documented, its mechanisms of action on the lung are known far less.
Hyperglycemia can lead to lung damage by increasing oxidative stresses and inflammation. Diabetes may be a trigger for pulmonary fibrosis, as studies suggest that there may be an important link between pulmonary fibrosis and diabetes.
In this review, the histopathological changes caused by diabetes in the lung tissue were summarized. In addition, changes in the lung due to inflammation, oxidative stress and pulmonary fibrosis mechanisms were evaluated.

Keywords: Lung, Diabetes mellitus, Fibrosis, Oxidative stress, Inflammation

INTRODUCTION

Diabetes develops as a result of a lack of / decreased insulin secretion, decreased insulin action, or decreased sensitivity of insulin receptors. Considering the etiology of the disease, immunological, genetic and environmental factors are known to be effective (1-3).

With a better understanding of the etiopathogenesis of diabetes mellitus, significant progress was made in respect of its classification and diagnosis. It can be classified as: type 1 diabetes, type 2, gestational and specific types of diabetes (4). Diabetes has different effects on many organs. Diabetes can cause complications such as retinopathy, nephropathy, neuropathy, cardiovascular and peripheral vascular diseases (5, 6). Diabetes is a disease that affects all systems associated with oxidative stress and inflammation (7). There is also evidence that diabetes affects the lungs (8, 9). In addition, patients with diabetes are at increased risk for other lung diseases (pneumonia, pulmonary fibrosis, etc.) (10, 11). However, functional abnormalities and

pathophysiologic changes in the lung tissue due to diabetes are ignored. Studies have shown that diabetes targets the lungs, alters their pathophysiology where inflammation is an important factor (12, 13). In addition, the deterioration of the oxidant/antioxidant balance is another factor (14). The lung has an extensive alveolar-capillary network (15). Studies examining the pathophysiological changes caused by diabetes have shown that diabetes causes hypoxia by causing a decrease in lung microvasculature, and that diabetes aggravates hypoxia in people with chronic lung disease (16, 17). These studies support that the lung is a structure affected by diabetic microangiopathy in diabetes (1, 15). Peripheral airway dysfunction has been demonstrated in type 1 diabetes (without other cause) (1). In addition, the interaction between diabetes and the Coronavirus Disease 2019 (COVID-19) was also investigated. The association between DM and poor outcome in patients with COVID-19 pneumonia was studied. These studies found that patients with diabetes are at heightened risk for severe COVID-19 symptoms (18). Patients with diabetes have a higher COVID-19-related mortality with severe COVID-19 symptoms being associated with ARDS (acute respiratory distress syndrome) and disease progression (19). For this reason, COVID-19 also poses a risk to diabetic patients, who should be monitored more closely. This leads scientists once again to understand the possible mechanism of action of diabetes on the lungs. In this review, the histopathological changes caused by diabetes in the lung tissue; lung function, oxidative stress, inflammation and fibrosis in diabetes are evaluated.

Lung Histology

The respiratory part of the lung consists of the respiratory bronchiole, alveolar duct, alveolar sac, and alveoli. The parts of the lung where gas exchange and respiration take place are the alveolar sacs. The histology of alveolar sacs is briefly as follows:

The alveolar epithelium contains type I pneumocytes, type II pneumocytes and brush cells. Besides these cells, there are also club cells and alveolar macrophages. Type I pneumocytes constitute the majority of the alveolar epithelium. They are flat, squamous epithelium resembling plate-like structures that allow gas exchange. Type II pneumocytes make up a smaller portion of the alveolar wall. Their numbers are low, but they are vital because they secrete pulmonary surfactant. Histologically, these cells have foamy cytoplasm resulting from surfactant. Type II pneumocytes are also mitotically active. Type II pneumocyte cells can be recognized by their rounded shape protruding into the alveolar space. Alveolar macrophages (or dust cells) may be free within the alveolar space or attached to the alveolar wall. If particles descend into the acini, macrophages are the last defenders of the respiratory epithelium (20).

Diabetes and Lung Histopathology

The histopathological changes caused by diabetes have been demonstrated clinically and in experimental models. The histopathological changes in the lung tissue of different living beings are as follows:

In an experimental study, rats induced with diabetes by streptozotocin (STZ) and rats administered bleomycin were studied for comparison and evaluation. There was lymphocyte infiltration, fibrosis, and organizing pneumonia in the STZ group. Focal alveolar damage and fibrosis were observed in the bleomycin group. For this reason, it was thought diabetes induced by STZ could cause pulmonary damage with organizing pneumonia (21). Another study revealed histopathologic findings such as thickness in the intralveolar septum of the lung tissue, lymphocyte infiltration, shedding in the bronchial epithelium and hyperemia (17). Light microscopic examination of rats with STZ-induced diabetes revealed changes in lung structure such as increased thickness of alveolar septa, high polymorphonuclear leukocytes (PMN) count in the alveolar wall, and increased lung fibrosis (22) (Figure 1). Similar histopathological findings were uncovered in the lungs of gerbils induced with diabetes with STZ (11). In addition to these findings, histopathologic examination of cats with diabetes revealed increased smooth muscle volume, mineralization, neoplasia, and pulmonary abnormalities such as increased type II pneumocyte count (23). Lungs from autopsied cases were compared for histopathologic examination in the diabetic and nondiabetic groups. Significant alveolar wall thickening was observed in diabetic patients. These studies suggest that histopathological changes in the lung (microangiopathy) may be a cause of pulmonary dysfunction (9). Diabetic and normal lung structures are as follows (Figure 1):

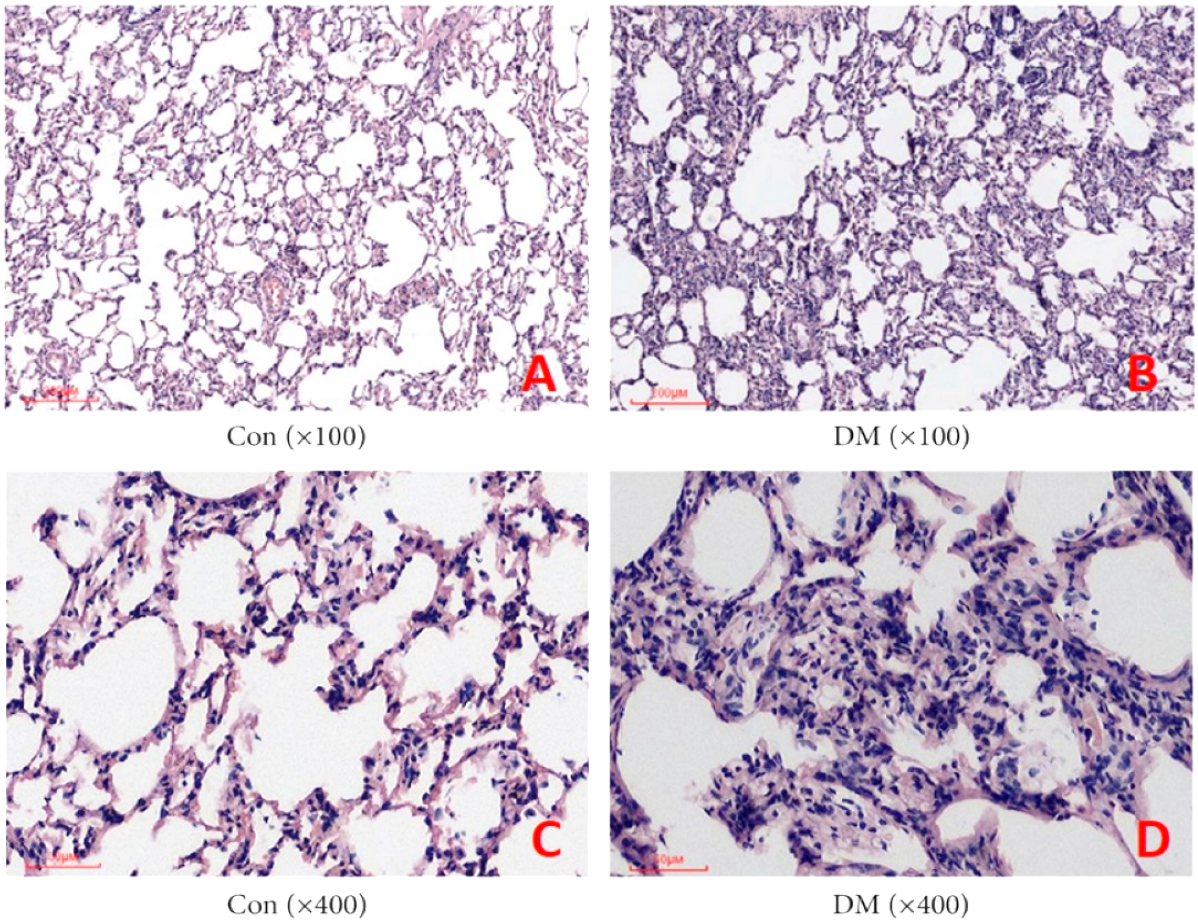

Figure 1. Lung tissue histopathological changes. A and C: healthy lung tissue (control (con) group); B and D: lung tissue with STZ-induced diabetes (Diabetes Mellitus (DM) group). Alveolar walls in the lung tissue in the control group (A and C) are of uniform shape and size. Hemorrhage and inflammatory infiltration are not observed. In the DM group, the alveolar septum was extensively thickened, inflammatory cell infiltration and hemorrhage occurred (hematoxylin-eosin) (24).

Lung Functions in Diabetes

Abnormalities due to functional changes in the lungs caused by diabetes have been revealed by studies (16, 22). These abnormalities manifest as decreases in elasticity, lung volume, and gas transfer (1). In diabetes, inflammatory infiltrates, edema, hemorrhage, and obstruction occur (25, 26). There are some data showing that microvascular reserve decreases and chronic hypoxia increases in the lungs of patients with diabetes. However, the underlying mechanism is not yet fully known. Due to the accumulation of collagen in the lungs, abnormalities such as stiffness may be observed in the lung parenchyma (17, 27, 28). It has been shown that diabetes causes significant decreases in pulmonary function levels measured by spirometry in patients (15, 29). A meta-analysis study examined data from respiratory function tests (PFT) performed on 3182 diabetic patients and 27,080 control group patients. The results showed impaired lung function. Pulmoner function levels were significantly reduced in patients with DM (30).

Diabetes and Pulmonary Fibrosis

Pulmonary fibrosis is a disease that can be defined by excessive proliferation of fibroblasts, increase in matrix proteins, accumulation of collagen in the tissue and epithelial cell damage. Pulmonary fibrosis generally has a high mortality rate (31).

Diabetes may be a trigger for pulmonary fibrosis, as studies suggest that there may be an important link between pulmonary fibrosis and diabetes; (10) however, the mechanisms underlying this link are still being studied. There is a link between hyperglycemia

and fibrosis, and the cellular pathways necessary to clearly explain this association are still being studied (21, 32).

An experimental study showed the presence of inflammatory cells in a histological analysis of diabetic patients. An increase in extracellular matrix was detected in the diabetic group, indicating the presence of tissue fibrosis (14).

Another experimental study showed that diabetes caused changes such as thickening of the alveolar septum, an increase in type II pneumocytes, and an increase in Hcy and cathepsin G levels in rats. These histopathologies and biochemical parameters indicate the presence of pulmonary fibrosis (22).

Wnt, a glycoprotein, controls many physiological events (tissue homeostasis, cell proliferation and migration, etc.). There are studies showing that the Wnt/β-catenin pathway plays a role in many tissue fibrosis as well as in pulmonary fibrosis. It is especially effective on processes such as epithelial mesenchymal transition and epithelial cell transformation (33-35).

In experimental models of pulmonary fibrosis, inhibition of the Wnt/β-catenin pathway has been reported to significantly improve pulmonary fibrosis. Therefore, the Wnt/GSK-3β/β-catenin pathway is thought to play an important role in the progression of pulmonary fibrosis (36, 37). In addition, another study found that silencing CIP4 (Cdc42-interacting protein-4) had a mitigating effect on STZ-induced pulmonary fibrosis. It was found that this was done by inhibition of the Wnt/GSK-3 β/β-catenin pathway (31).

Diabetes, Lung, Oxidative Stress and Inflammation

Hyperglycemia can lead to lung damage by increasing oxidative stresses and inflammation (38). Mechanisms explaining such diabetes-induced lung tissue damage include: increased glucose influx via polyol, increased advanced glycation end products (AGEs) in the cytoplasm, protein kinase C isoform activation, and hexosamine pathway activation. It is estimated that the activation of these mechanisms may be due to the increase in mitochondrial reactive oxygen species (17, 39). Looking at oxidative stress associated with diabetes, several studies show that the formation of free radicals due to hyperglycemia and thus oxidative stress causes diabetes-related complications (40). Also, the mechanisms through which deterioration in glycemic control can lead to a decline in pulmonary function may also progress with systemic inflammation (41).

PMN (polymorphonuclear leukocytes) leukocytes play an important role in lung defense. When activated, PMN cells secrete reactive oxygen species, some proteolytic enzymes and cytotoxic substances such as chemokines and cytokines. This can damage the lung and cause acute inflammation (22, 42, 43).

In short, ROS increases inflammation by stimulating some enzymes whose activity increases due to stress. ROS can induce proinflammatory cytokine expression by stimulating transcription factors (for instance, nuclear factor kappa B (NF-kB) (44). It is thought that TNF-α may also play a role in diabetes. TNF-α, which activates intracellular NF-kB, regulates adhesion molecules and increases oxidative stress. In this way, oxidative stress can cause a stimulus pathway to affect glucose metabolism (45, 46).

Chronic hyperglycemia can also cause an increase in collagen molecule synthesis due to the increase in advanced glycation end products, which can negatively affect the lung and its functions (45). Therefore, targeting oxidative stress and inflammatory cytokine signaling pathways is predicted to be suitable for the treatment of diabetes (44).

An increase in pulmonary oxidative stress is known to be observed in rats with streptozotocin-induced DM. These effects may be due to the action of free radicals on cell membrane structures in lung tissue (47). Examination of lung tissue from rats with DM using an electron microscope revealed that it had ultrastructural alterations such as increased basement membrane thickness, increased pulmonary fibrosis, and abnormalities with type II pneumocytes. It has been demonstrated that administration of exogenous SOD to these rats restored the ultrastructure of the lung tissue to near-normal state (48).

NLRP3 Inflammation

Chronic diseases can produce cellular or metabolic inflammation. However, it is thought that the opposite of this, namely inflammation, also affects the formation and progression of chronic diseases. Increasing evidence has shown an association between diabetes mellitus and chronic inflammation caused by high levels of proinflammatory cytokines (49). For this reason, NLRP3 (NOD-like receptor family pyrin domain-containing protein 3), which is

one of the intracellular receptors involved in the inflammatory response, and the inflammasome complex it forms are thought to be associated with diseases. Pathogen-related stimuli or non-pathogen stimuli induce or suppress the NLRP3 inflammasome in the formation of an inflammatory response (50). In response to these stimuli, caspase1 is activated. Activated caspase-1 also activates the precursor forms of the cytokines IL-1β (interleukin-1β) and IL-18 (interleukin-18). Thus, inflammatory responses mediated by IL-1β and IL-18 are activated. Although NLPR3 activation is important for the immune response, its overactivation can cause inflammatory diseases and cell death (51).

In a study, it was found that NLRP3 mRNA was expressed at the highest level in the lung after the spleen (52). Pulmonary macrophages and lung epithelial cells express NLRP3 and produce IL-1β in response to various stimuli (53). It is known that NLRP3 plays a role in various lung pathologies (54).

Activation of the NLRP3 inflammasome is thought to contribute to many inflammatory conditions. It is suggested that the NLRP3 inflammasome also plays a key role in the development of DM. It is known that NLRP3 inflammation participates in transformed growth factor β1, bleomycin-induced pulmonary inflammation and fibrosis (55,56), indicating that pulmonary fibrosis and NLRP3 inflammation are closely related (57). Pulmonary fibrosis accompanied by an increase in NLRP3 in the lungs was observed in a rat DM model lasting 12 weeks (58). In a rat model of DM, increased lung NLRP3 inflammatory, NLRP3 and caspase-1 protein expressions and pulmonary fibrosis in the lung were observed at both the sixth and twelfth weeks. It has also been implicated in diabetes-induced lung damage throughout the course of the disease, not just at the onset of diabetes. Inflammation is thought to be an important cause of pulmonary fibrosis (57).

NLRP3 has been shown to be activated in various tissue damages associated with DM (54,59,60). In addition, it is known that NLRP3 plays a role in various lung pathologies (54). Fibrosis can be seen in the lungs in DM. NLRP3 inflammasome plays a very important role in pulmonary fibrosis. Conducting new studies on NLRP3 inflammasome in lung pathology associated with DM may be promising for future treatments.

CONCLUSION

Chronic hyperglycemia can cause functional damage or failure in many organs. While damage to the lung caused by hyperglycemia can be overlooked.

Histopathological changes such as thickening of alveolar septa, increase in PMN in the alveolar wall, and increase in pulmonary fibrosis were observed in experimental animals induced with diabetes. It is known that formation of free radicals due to hyperglycemia, resulting in oxidative stress and inflammation, can cause diabetes and related complications. It is important to clarify the pathways by which oxidative stress and inflammation in diabetes exert their damaging impact on lung tissue.

This review examined the mechanisms of diabetes leading to histopathological changes, oxidative stress, and inflammation in lung tissue. We believe that oxidative damage due to hyperglycemia and pathophysiological mechanisms associated with inflammation should be considered in diabetic patients as well as in patients with COVID-19 in particular, with regards to lung damage.

Acknowledgments: None.
Author contribution: ABY, DY, EK: Writing the manuscript, editing the manuscript and collection of data. NK: Review of the literature and collection of data. ATA, TC: Review of the literature. EÖ: Collection of data.
Conflict of interests: No conflict of interest was declared by the authors.
Ethical approval: None.
Funding: None.
Peer-review: Externally peer-reviewed.

REFERENCES

1. Goldman MD. Lung dysfunction in diabetes. Diabetes care. 2003;26(6):1915-8.
2. Pitocco D, Fuso L, Conte EG, Zaccardi F, Condoluci C, Scavone G, et al. The diabetic lung-a new target organ? Rev Diabet Stud 2012;9(1):23.
3. Erdoğan BB, Uzaslan E. Diabetes and lung. Journal of Uludag University Faculty of Medicine 2005. 31;(1):71-74.
4. Ramachandran A, Snehalatha C, Nanditha A. Classification and diagnosis of diabetes. In Holt RICockram CSFlyvbjerg A, Goldstein BJ, editors. Textbook of diabetes. 5th ed. Oxford, UK: Wiley-Blackwell; 2017. p. 23–8.
5. Zhang RH, Cai YH, Shu LP, Yang J, Qi L, Han M, et al. Bidirectional relationship between diabetes and pulmonary function: a systematic review and meta-analysis. Diabetes Metab. 2020:101186.

6. Nathan DM. Diabetes: advances in diagnosis and treatment. Jama 2015;314(10):1052-62.
7. Khateeb J, Fuchs E, Khamaisi M. Diabetes and lung disease: a neglected relationship Rev Diabet Stud 2019;15:1.
8. Kinney GL, Black-Shinn JL, Wan ES, Make B, Regan E, Lutz S, et al. Pulmonary function reduction in diabetes with and without chronic obstructive pulmonary disease. Diabetes care 2014;37(2):389-95.
9. Matsubara T, Hara F. The pulmonary function and histopathological studies of the lung in diabetes mellitus. Nihon Ika Daigaku Zasshi 1991;58(5):528-36.
10. Ehrlich SF, Quesenberry CP, Van Den Eeden SK, Shan J, Ferrara A. Patients diagnosed with diabetes are at increased risk for asthma, chronic obstructive pulmonary disease, pulmonary fibrosis, and pneumonia but not lung cancer. Diabetes care 2010;33(1):55-60.
11. Chen CM, Juan SH, Pai MH, Chou HC. Hyperglycemia induces epithelial–mesenchymal transition in the lungs of experimental diabetes mellitus. Acta histochem 2018;120(6):525-33.
12. Honiden S, Gong MN. Diabetes, insulin, and development of acute lung injury. Crit. Care Med 2009;37(8):2455.
13. Mannino DM, Ford ES, Redd SC. Obstructive and restrictive lung disease and markers of inflammation: data from the Third National Health and Nutrition Examination. Am J Med 2003;114(9):758-62.
14. Di Naso FC, Forgiarini Júnior LA, Forgiarini LF, Porawski M, Dias AS, Marroni NAP. Aminoguanidine reduces oxidative stress and structural lung changes in experimental diabetes mellitus. J Bras Pneumol 2010; 36, 485-489.
15. Klein O, Krishnan J, Glick S, Smith L. Systematic review of the association between lung function and Type 2 diabetes mellitus. Diabetic Med 2010;27(9):977-87.
16. Hsia CC, Raskin P. Lung function changes related to diabetes mellitus. Diabetes Technol. Ther. 2007;9(S1):S-73-S-82.
17. Onk D, Onk OA, Erol HS, Özkaraca M, Çomaklı S, Ayazoğlu TA, et al. Effect of melatonin on antioxidant capacity, ınflammation and apoptotic cell death in lung tissue of diabetic rats. Acta Cir. Bras 2018;33:375-85.
18. Guo W, Li M, Dong Y, Zhou H, Zhang Z, Tian C, et al. Diabetes is a risk factor for the progression and prognosis of COVID-19. Diabetes Metab. Res. Rev 2020;36(7):e3319.
19. Huang I, Lim MA, Pranata R. Diabetes mellitus is associated with increased mortality and severity of disease in COVID-19 pneumonia–a systematic review, meta-analysis, and meta-regression. Diabetes Metab Syndr 2020;14(4):395-403.
20. Khan YS, Lynch DT. Histology, lung. StatPearls Publishing 2018.
21. Wang CM, Hsu CT, Niu HS, Chang CH, Cheng JT, Shieh JM. Lung damage induced by hyperglycemia in diabetic rats: The role of signal transducer and activator of transcription 3 (STAT3). J. Diabetes Complicat 2016;30(8):1426-33.
22. Alireza S, Leila N, Siamak S, Mohammad-Hasan KA, Behrouz I. Effects of vitamin E on pathological changes induced by diabetes in rat lungs. Respir Physiol Neurobiol 2013;185(3):593-9.
23. Mexas AM, Hess RS, Hawkins EC, Martin LD. Pulmonary lesions in cats with diabetes mellitus. J. Vet. Intern. Med 2006;20(1):47-51.
24. Hu JF, Zhang GJ, Wang L, Kang PF, Li J, Wang HJ, et al. Ethanol at low concentration attenuates diabetes induced lung injury in rats model. Journal of Diabetes Research 2014.
25. Weynand B, Jonckheere A, Frans A, Rahier J. Diabetes mellitus induces a thickening of the pulmonary basal lamina. Respiration 1999;66(1):14-9.
26. Medeiros TDD, Pereira AT, Silva FSD, Bortolin RH, Taveira KVM, et al. Ethanol extract of Cissampelos sympodialis ameliorates lung tissue damage in streptozotocin-induced diabetic rats. Braz. J. Pharm. Sci 2020;56.
27. Lazarus R, Sparrow D, Weiss ST. Handgrip strength and insulin levels: cross-sectional and prospective associations in the Normative Aging Study. Metabolism 1997;46(11):1266-9.
28. Ofuwe AF, Kida K, Thurlbeck WM. Experimental diabetes and the lung. Am Rev Respir Dis. 1988; 137(1),162-66.
29. Klein OL, Kalhan R, Williams M, Tipping M, Lee J, Peng J, et al. Lung spirometry parameters and diffusion capacity are decreased in patients with Type 2 diabetes. Diabetic Med 2012;29(2):212-9.
30. Rajasurya V, Gunasekaran K, Surani S. Interstitial lung disease and diabetes. World J. Diabetes 2020;11(8):351.
31. Zhang X, Liu Y, Shao R, Li W. Cdc42-interacting protein 4 silencing relieves pulmonary fibrosis in STZ-

induced diabetic mice via the Wnt/GSK-3β/β-catenin pathway. Exp. Cell Res 2017;359(1):284-90.
32. Li Y, Ma J, Zhu H, Singh M, Hill D, Greer PA, et al. Targeted inhibition of calpain reduces myocardial hypertrophy and fibrosis in mouse models of type 1 diabetes. Diabetes 2011;60(11):2985-94.
33. Chilosi M, Poletti V, Zamò A, Lestani M, Montagna L, Piccoli P, et al. Aberrant Wnt/β-catenin pathway activation in idiopathic pulmonary fibrosis. Am. J. Clin. Pathol 2003;162(5):1495-502.
34. Flozak AS, Lam AP, Russell S, Jain M, Peled ON, Sheppard KA, et al. β-catenin/T-cell factor signaling is activated during lung injury and promotes the survival and migration of alveolar epithelial cells. J. Biol. Chem 2010;285(5):3157-67.
35. Kneidinger N, Yildirim AON, Callegari J, Takenaka S, Stein MM, Dumitrascu R, et al. Activation of the WNT/β-catenin pathway attenuates experimental emphysema. Am. J. Respir. Crit. Care Med 2011;183(6):723-33.
36. van Noort M, Meeldijk J, van der Zee R, Destree O, Clevers H. Wnt signaling controls the phosphorylation status of β-catenin. J. Biol. Chem 2002;277(20):17901-5.
37. Chen X, Shi C, Meng X, Zhang K, Li X, Wang C, et al. Inhibition of Wnt/β-catenin signaling suppresses bleomycin-induced pulmonary fibrosis by attenuating the expression of TGF-β1 and FGF-2. Exp. Mol. Pathol 2016;101(1):22-30.
38. Lee J-Y, Jeon I, Lee JM, Yoon J-M, Park SM. Diabetes mellitus as an independent risk factor for lung cancer: a meta-analysis of observational studies. Eur J Cancer 2013;49(10):2411-23.
39. Brownlee M. The pathobiology of diabetic complications: a unifying mechanism. Diabetes 2005;54(6):1615-25.
40. Haskins K, Bradley B, Powers K, Fadok V, Flores S, Ling X, et al. Oxidative stress in type 1 diabetes. Ann. N. Y. Acad. Sci 2003;1005(1):43-54.
41. Lange P, Parner J, Schnohr P, Jensen G. Copenhagen City Heart Study: longitudinal analysis of ventilatory capacity in diabetic and nondiabetic adults. Eur Respir J 2002;20(6):1406-12.
42. Lee WL, Downey GP. Neutrophil activation and acute lung injury. Curr Opin Crit Care 2001;7(1):1-7.
43. Reinhart PG, Bassett DJ, Bhalla DK. The influence of polymorphonuclear leukocytes on altered pulmonary epithelial permeability during ozone exposure. Toxicology. 1998;127(1-3):17-28.
44. Oguntibeju OO. Type 2 diabetes mellitus, oxidative stress and inflammation: examining the links. International journal of physiology, pathophysiology and pharmacology. 2019;11(3):45.
45. Tiengo A, Fadini G, Avogaro A. The metabolic syndrome, diabetes and lung dysfunction. Diabetes Metab 2008;34(5):447-54.
46. Sonnenberg GE, Krakower GR, Kissebah AH. A novel pathway to the manifestations of metabolic syndrome. Obes Res 2004;12(2):180-6.
47. Gumieniczek A, Hopkała H, Wójtowicz Z, Wysocka M. Changes in antioxidant status of lung tissue in experimental diabetes in rabbits. Clin. Biochem 2002;35(2):147-9.
48. Forgiarini Junior LA, Kretzmann NA, Tieppo J, Picada JN, Dias AS, Marroni NAP. Lung alterations in a rat model of diabetes mellitus: effects of antioxidant therapy. J. Bras. Pneumol 2010;36:579-87.
49. Özenver N, Efferth T. Phytochemical inhibitors of the NLRP3 inflammasome for the treatment of inflammatory diseases. Pharmacological Research 2021;170, 105710.
50. Arman G, Ünal RN. Inflammation in diabetes and atherosclerosis: relationship between macro/micronutrients and the NLRP3 inflammasome. Kafkas Journal of Medical Science 2021;11(2), 336-349.
51.Şaker D, Polat S. An Overview of NLRP3 Inflammasome Activation and Regulation Mechanisms. Archives Medical Review Journal 2022;31(1), 52-59.
52.Guarda G, Zenger M, Yazdi AS, Schroder K, Ferrero I, Menu P, et al. Differential expression of NLRP3 among hematopoietic cells. The Journal of Immunology 2011;186(4), 2529-2534.
53. Tran HB, Lewis MD, Tan LW, Lester SE, Baker LM, Ng J, et al. Immunolocalization of NLRP3 inflammasome in normal murine airway epithelium and changes following induction of ovalbumin-induced airway inflammation. Journal of allergy; 2012.
54.De Nardo D, De Nardo CM, Latz E. New insights into mechanisms controlling the NLRP3 inflammasome and its role in lung disease. The American journal of pathology 2014;184(1), 42-54.
55. Liang Q, Cai W, Zhao Y, Xu H, Tang H, Chen D, et al. Lycorine ameliorates bleomycin-induced pulmonary fibrosis via inhibiting NLRP3 inflammasome activation and pyroptosis. Pharmacol Res. 2020;158: 104884.
56. Zheng R, Tao L, Jian H, Chang Y, Cheng Y, Feng Y, et al. NLRP3 inflammasome activation and lung

fibrosis caused by airborne fine particulate matter. Ecotoxicol Environ Saf. 2018;163: 612–619.
57.Wang W, Cao Z, Liang H, Zhao C, Gong B, Hu J. Effect of low-dose ethanol on NLRP3 inflammasome in diabetes-induced lung injury. Experimental Animals 2021;70(3), 364-371.
58. Chen Y, Zhang F, Wang D, Li L, Si H, Wang C, et al. Mesenchymal Stem Cells Attenuate Diabetic Lung Fibrosis via Adjusting Sirt3-Mediated Stress Responses in Rats. Oxid Med Cell Longev. 2020; 2020: 8076105.
59. Bilen A, Calik I, Yayla M, Dincer B, Tavaci T, Cinar I, et al. Does daily fasting shielding kidney on hyperglycemia-related inflammatory cytokine via TNF-α, NLRP3, TGF-β1 and VCAM-1 mRNA expression. International Journal of Biological Macromolecules 2021;190, 911-918.
60. Ge K, Wang Y, Li P, Li M, Zhang W, Dan H, et al. Down-expression of the NLRP3 inflammasome delays the progression of diabetic retinopathy. Microvascular Research 2022, 139, 104265.